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Review Article

The Psychiatric implications of the Gut -Brain interactions

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Abstract

The gut microbiota is currently being considered as a key regulator of the gut-brain axis. The interactions between the gut microbiota and the brain are being implicated as an important factor in the etiology and treatment of various psychiatric disorders. This review summarizes the current knowledge about the role of the gut-brain axis in autism spectrum disorder, cognitive frailty and Alzheimer's disease, schizophrenia, depression, anxiety, posttraumatic stress disorder, obsessive compulsive disorder, eating disorders and substance use disorders. Although considerable progress has been made in the understanding of the enteric nervous system and the microbiota-gut-brain axis in preclinical models of diseases, more randomized clinical trials with larger population are necessary before implementing these findings as an essential component of comprehensive diagnostic assessments and rendered as potential alternative therapeutic interventions.

Keywords: Gut Microbiota; Gut-Brain-Axis; Enteric Nervous System; Psychiatric Disorders; Alternative Treatments.

Introduction

Recent and ongoing animal and pre-clinical human research have recognized important interactions between the gut and the brain and underscored the clinical relevance of these interactions. The enteric nervous system (ENS) constitutes a substantial portion of the autonomic nervous system (ANS) and is specifically occupied with microcircuits that influence gastrointestinal (GI) activities unfettered from the central nervous system (CNS) [1,2]. Subsequent transmission from the brain to the gut occurs through the multiple pathways of the vagus nerve at the frequency of milliseconds. This relatively high-speed transmission plays an essential role in the GI tract activities [3]. The effects of the gut microbiome on the brain have been attributed to various factors including the anatomical distributions of the vagus nerve as it travels through the gut-brain axis and the hormonal influences of the endocrine glands through the hypothalamic-pituitary-adrenal (HPA) axis. The metabolic products of certain pathogenic microbiota could also alter the integrity of the gut immune system, leading to leakage from the intestinal mucosa into the blood circulation and ultimately crossing the blood- brain barrier as illustrated in figure 1.

The ENS neural tissue in the gut produces over 30 different neurotransmitters including serotonin, gamma-aminobutyric acid (GABA), dopamine, acetylcholine, and noradrenaline [4]. When these constantly interacting systems go awry, diseases of the gut and the brain could develop as demonstrated in figure 2.

This review summarizes the functions of the microbiota, the microbiota-gut -brain(MGB), the ENS, and the vagus nerve. The psychiatric manifestations that could emerge as a consequence of

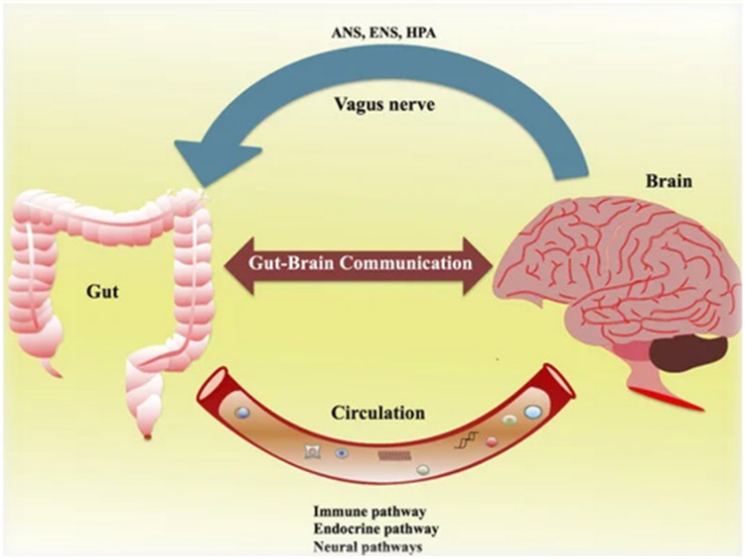

Figure 1: Illustration of the various components and interactions of the Gut-Brain Axis.

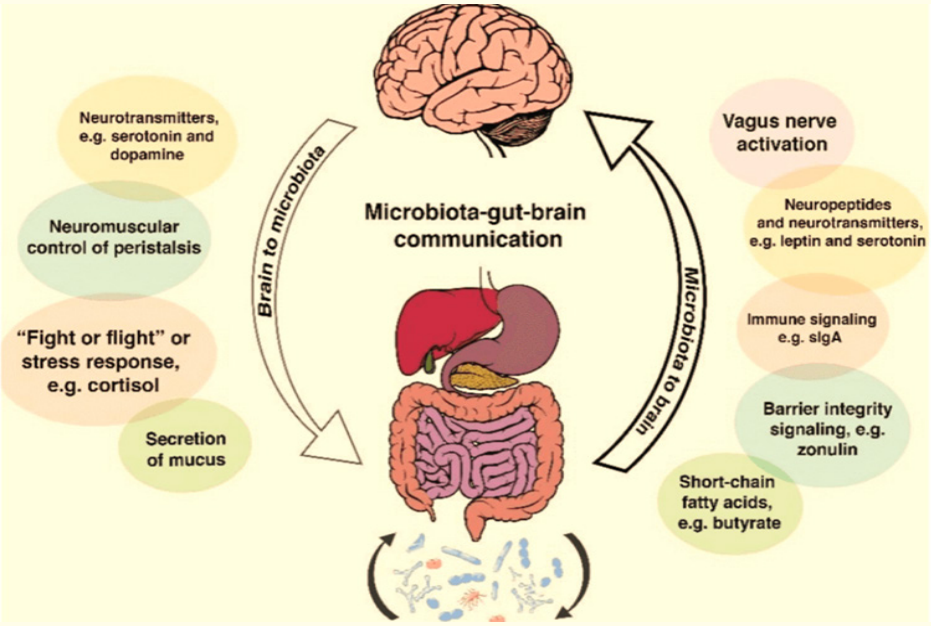

Figure 2: Hypothetical demonstration of the microbiota Gut-Brain communications.

gut-brain dysfunctional include effects on several conditions [5] such as autism spectrum disorder, cognitive frailty and Alzheimer's disease, schizophrenia, depression, anxiety, posttraumatic stress disorder, obsessive compulsive disorder, eating disorders and substance use disorders.

Gut microbiota

It is estimated that gut microbiota approximately weighs 1-2 kg which coincidently equals the average weight of a normal adult human brain [6]. The gut microbiome is roughly inhabited by beneficial 100 trillion organisms including bacteria, viruses, fungi, and archaea which are influenced by the harmful effects of pathogens which could alter the functioning of the immune system and may cause disturbance of metabolic homeostasis leading to ENS pathogenesis and the development of behavioral and psychiatric disorders. Initial establishment of the human gut microbiota is generally believed to occur immediately following birth. Then through its development the brain is influenced by gut microbiota interactions with the HPA axis and its role in modulating the stress response of fight, flight or freeze and its subsequent effects on mood, anxiety and cognitive functioning [7]. The human gut microbiota are also actively engaged in the release of multiple chemicals such as cytokines, neuropeptides, chemokines, short-chain fatty acids (SCFAs), branched chain amino acids, and peptidoglycans [8], with certain microbiomes consuming while other producing an array of neurotransmitters, dedicated research is needed to delineate and differentiate between harmful and beneficial microbiota to determine the physiological implications of microbiota-mediated manipulation of neurotransmission and their therapeutic outcomes in humans.

Microbiota-gut-brain axis

The microbiota-gut-brain (MGB) axis is a two-way reciprocal transmission system that involves communication between the GI tract the CNS, the [9]. Endocrine glands, the immune systems, the HPA axis, the sympathetic and parasympathetic components of the autonomic nervous system (ANS), the ENS, the vagus nerve, and the gut microbiota [1,4,7-9]. The MGB interactions with the hippocampus, the amygdala and the prefrontal cortex also exert an effect on emotional responses and their behavioral expressions [10].

Enteric nervous system

The enteric nervous system (ENS) is sometimes called the "second brain" based on the notion that during fetal development, it stems from the same cells as those of the CNS and many of its structural components and chemical secretions are analogous to those of the brain. As such the ENS is considered an intricate component of a neural network that involves the endocrine HPA axis, the immune system functioning and the various neurotransmitter pathways [11]. The intricate interactions between the ANS, ENS, the microbial metabolites, the HPA, the vagus nerve and the gut brain axis are summarized in figure 3.

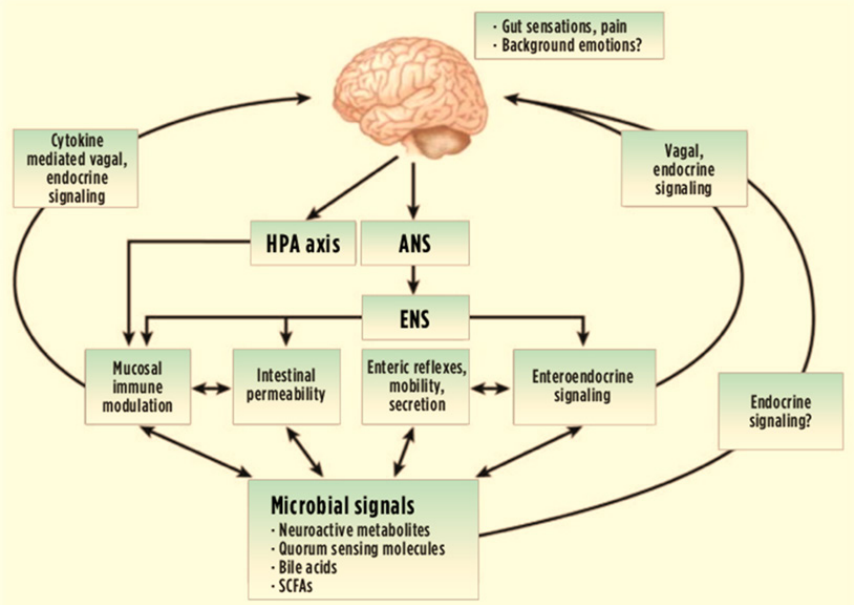

Figure 3: Interactions between the Gut-Brain axis, ANS, ENS, and the HPA.

Psychiatric manifestations of the gut -brain connection

As previously described recent and ongoing research have documented the role of the gut microbiota in regulating the integrity and the function of the human gut and its subsequent effects on biological homeostasis and the overall general health [12]. Preliminary evidence suggests that the gut microbiota impact extend to many biological systems including the central nervous system (CNS) [13]. The gut microbiota alteration or dysbiosis, is hypothesized to influence the brain activity and its behavioral manifestations through various pathways that encompass the neural, endocrine, and immune systems [14]. Such an alteration in the composition of the gut microbiome has been linked to the development and progression of neurological, cognitive and psychiatric disorders [14]. Most of the neurodevelopmental and neurodegenerative disorders attributed to the gut-brain bidirectional are beyond the scope of this review which mainly focus on the psychiatric disorders such as autism spectrum disorder, cognitive frailty and dementia, depression, schizophrenia, posttraumatic stress disorder, obsessive compulsive disorder, eating disorders and substance use disorders which could have been precipitated by gut microbiome imbalance and could be subsequently treated by restoring the microbiome balance [9,10].

Autism spectrum disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder usually manifested by psychological and social complications that encompass difficulties in social communication with rigid, restricted, repetitive patterns of peculiar behaviors, odd interests, or stereotyped activities. Although 0.1% to 1.8% of the global population could be affected by ASD, its cause and pathogenesis remain unidentified and is hypothesized to be a result of a complex interaction between abnormal brain function with genetic and environmental underpinnings [15]. Many patients with ASD experience disturbances in GI functioning manifested by diarrhea or constipation. Preclinical human research trials found the GI disturbances to be due to an imbalance in the gut microbiota and their subsequent effects on the gut-brain communications [16]. It is plausible that future research that focus on discovering the microbiome-gut -brain interactions in ASD, could pave the way on developing treatment interventions such as probiotics and fecal microbiota transplant. These microbiota-targeted treatment eventually lead to the amelioration of the behavioral and the GI disturbances in individuals with ASD.

Cognitive frailty and dementia

Generally, the term frailty is defined as a complex and multifaceted clinical syndrome. In clinical settings cognitive frailty is a sub could represent a precursor of neurodegenerative conditions such as dementia and Alzheimer's disease (AD), which is the most prevalent cause of dementia in the elderly populations [17]. Aging could affect the gut in various ways including thinning of the gut walls and inflammation, increased permeability and dumping of gut microbiota into the circulation and crossing the blood-brain barrier. Unbalanced gut microbiota and dysbiosis would promote the development of beta-amyloid (Aβ) plaques and neurofibrillary tangles which have been implicated as precursors for the neurodegenerative process that lead to the development of dementia and AD. Preclinical research that is designed with the goal of understanding the link between the aging gut, dysbiosis and inflammatory process could unlock the role of modifying the gut microbial composition in possibly preventing and ultimately treating the neurodegenerative process of dementia and AD [18].

Schizophrenia

Many patients with schizophrenia have been found in various studies to have alterations in gut microbiota that are linked to inflammatory changes [19]. The alterations in microbiome in schizophrenia are considered inadequate to establish a link to an increased risk of developing that illness and require more depth preclinical trials [20]. The manipulation of gut microbiomes with probiotics and prebiotics as adjunctive or alternative treatments in schizophrenia is still undetermined and inconclusive and would require further research and more clinical trials to test the validity of manipulating the gut microbiome to improve the treatment of this chronic debilitating disorder.

Depression

Despite the availability of multiple treatment modalities for the treatment of depression, many patients do not respond to treatment and other discontinue treatment due to recurrence of adverse effects [21]. There is a need to develop new hypothesis-driven treatment for depression. Major depressive disorder (MDD) has also been associated with poor illness outcomes, and less adherence treatment. The combination of psychotherapy and antidepressant medications seem to be effective in managing 33% to 44% of patients with MDD, with the remainder of patients still unresponsive to the currently available treatment interventions [21]. Microbiota alterations with probiotics could be explored as an alternative or adjunctive treatment modalities for MDD [22]. The relative low risk for side effects with probiotics compared to the conventional antidepressant array of side effects could offer a beneficial advantage for those who discontinue antidepressants treatment due to their adverse effects [23]. Despite the general

support for a plausible probiotic antidepressant effect, there still is a paucity of randomized clinical trials to confirm the validity of this intervention as a beneficial treatment for MDD [24].

Anxiety

Anxiety disorders are among the most common psychiatric conditions and affect nearly 30% of adults at some point in their lives. Many effective interventions are available to treat anxiety including evidence-based psychotherapies, several antidepressants and anxiolytics. These treatment modalities help most patients with anxiety disorders in attaining a normal and productive levels of daily functioning lives [25]. Ongoing animal and clinical studies aimed at understanding the microbiota-gut-brain axis role in developing anxiety have identified a relationship between stress and microbiota, and that alterations in microbiota due to stress could influence the development and progression of anxiety disorder due to its effects on the blood-brain barrier (BBB), also in causing immune dysregulation, and modification of autonomic sensorimotor connections, and the hypothalamus-pituitary-adrenal axis [26]. The role of probiotics supplementation in influencing the gut-brain-microbiome interactions along with its various communication pathways could be explored as potential agents to-improve and reverse symptoms of treatment refractory anxiety disorders [28]. In that context, factors related to treatment duration, specific probiotics and their possible interactions with the brain have not been thoroughly investigated and deserve more meta-analysis of controlled clinical trials [29].

Posttraumatic stress disorder

The conventional treatment of posttraumatic stress disorder (PTSD) usually combines psychotherapy, pharmacotherapy and many individuals receiving ongoing treatment do improve, however some continue to exhibit persistence of PTSD symptoms and discontinue treatment due to the lack of effectiveness, the slow pharmacotherapy onset of action or the burden of their side effects [30]. Increasing research on the bidirectional signaling between the gut and the brain has drawn attention to plausible links between the development of PTSD and the gut lower microbial diversity [31]. Available clinical data that demonstrate a connection between the microbiome and the susceptibility or resilience to the early life development of PTSD is still scare and limited [32]. Some experimental and clinical data have shown that imbalances in the gut microbiota may exert physiologic effects and predispose to a susceptibility for developing PTSD in the aftermath of traumatic events and suggesting that it may be possible that altering gut bacteria either by supplementation or by dietary changes could be established as alternative PTSD treatment approaches [33]. The discovery of certain strains of bacteria that have shown effects on enhancing cognitive processes and diminishing fear learning in animal models also lend support to this concept [34]. Additional research is still needed to identify the specific microbiomes that would achieve long term beneficial effects especially in treatment resistant PTSD.

Obsessive compulsive disorder

Obsessive compulsive disorder (OCD) is a debilitating complex disorder with still unknown definitive cause and treatment options that are modestly beneficial [35,36]. The bidirectional microbiota-gut-brain axis has been implicated in etiological pathway of OCD [37] An imbalance in the gut and oropharyngeal microbiomes have also been detected in some patients with OCD [38]. Additionally gut microbiome and inflammation have also been identified in OCD cases [39]. These findings suggest that an alternative treatment could be aimed at the introduction of beneficial gut microbiome as a remediation strategy in OCD patients and particularly those with gut inflammation that caused microbiome imbalance [40]. Based on the current evidence, a possible contribution of different types of microbes has been proposed for the development of OCD. However, the currently available literature is still inconclusive [41]. Therefore, further studies are needed to better understand the impact of microbiota dysbiosis on the development and progression of OCD [37].

Eating disorders

The link between imbalance of the gut microbiome and the development of eating disorders has been examined in animal and human studies [42]. The effects of the gut microbiomes imbalance on body weight, vulnerability to obesity and to the development of various eating disorders have been reported in several research trials [43]. Several studies have also shown that alteration of the gut microbiota through diet, probiotics supplementation or fecal transplantation could have an impact on regulating the pervasive caloric restriction in anorexia nervosa and the uncontrollable binge eating in bulimia nervosa and binge eating disorder [44]. Preclinical trials have concluded that the preservation of gut permeability and the prevention of gut inflammation and their immune reactions are

usually associated with a well-balanced domain of gut microbiome. Gut dysbiosis could tip the delicate equilibrium that regulates the hunger drive and the brain satiety center and would trigger pathophysiological reactions that are considered salient ingredients for the development of eating disorders [45]. These findings suggest that the restoration of the gut microbiomes dysbiosis could be an alternative treatment option for eating disorders however, that need to be confirmed by conducting future randomized and placebo controlled clinical trials with a larger population sample [45].

Substance use disorders

As a global and worldwide challenging public health concern, substance use disorders (SUDs) are complex conditions due to their frequent co-occurrences with medical and psychiatric disorders. In clinical practice SUDs involve several different substances including, stimulants, cocaine, opiates, cannabinoids, nicotine, alcohol, and multiple synthetic agents. Effective treatments for substance use disorders are readily available with an essential focus on the psychological and biological components of SUD and addictions. The gut microbiota could be affected by the intake of the various substances of abuse and dysbiosis could be one of the elements contributing to the development SUDs and their treatment [46]. Studies have indicated that the imbalance of the gut microbiomes as a consequence of SUDs and addictions could influence the gut-brain axis communication leading to the maintenance of addiction [46,47]. Therefore, there is a dire need for more randomized controlled clinical trials to untangle and understand the interplay of gut microbiome in the development and therapeutic intervention in SUDs [47].

Discussion and Conclusion

There is increasing interest in the role of the gut microbiota in the maintenance of health and the development of medical and mental diseases. The various interaction between the gut microbiome through the gut-brain axis via the vagus pathways is extensive and involves the CNS, the ANS, the ENS and the HPA axis. The effects of the gut microbiome on the brain has been attributed to various factors beyond the anatomical pathways of the vagus nerve encompassing the GI tract permeability, induction of an immunological response to gut inflammation and the crossing of the blood-brain barrier. A dysfunction within the gut -brain axis, and microbiome dysbiosis, could impact brain functioning and subsequently contribute to the development of various psychiatric disorders. Additionally the alteration of gut dysbiosis could be a novel or an adjunctive treatment of various psychiatric disorders such as autism spectrum disorder, cognitive frailty and Alzheimer's disease, schizophrenia, depression, anxiety, posttraumatic stress disorder, obsessive compulsive disorder, eating disorders and substance use disorders. Animals and preclinical human research have widened the understanding of the ENS referred to as "the second brain" and the microbiota-gut-brain axis. More randomized clinical trials with larger population are necessary before implementing these findings as a component of comprehensive psychiatric assessment and prior to their consideration as potential alternative treatment interventions.

Conflict of Interests

The materials described in this article are those of the authors and do not reflect the views of the Department of Veterans Affairs, the VA Central California Health Care System, or the UCSF Fresno Medical Education Program, California.

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Bibliography

1. Almeida C., *et al*. "Influence of gut microbiota dysbiosis on brain function: a systematic review". *Porto Biomedical Journal* 5.2 (2020): 1-8.

2. Grundy D and Schemann M. "Enteric nervous system". *Current Opinion in Gastroenterology* 23.2 (2007): 121-126.

3. Bonaz B., *et al*. "The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis". *Frontiers in Neuroscience* 12 (2018): 49.

4. Strandwitz P. "Neurotransmitter modulation by the gut microbiota". *Brain Research* 1693.Pt B (2018): 128-133.

5. Ansari F., *et al*. "The Effects of Probiotics and Prebiotics on Mental Disorders: A Review on Depression, Anxiety, Alzheimer, and autism spectrum disorders". *Current Pharmaceutical Biotechnology* 21.7 (2020): 555-565.

6. Sender R., *et al*. "Revised Estimates for the Number of Human and Bacteria Cells in the Body". *PLOS Biology* 14.8 (2016).

7. Foster JA., *et al*. "Stress and the gut-brain axis: Regulation by the microbiome". *Neurobiology of Stress* 7 (2017): 124-136.

8. Cryan JF., *et al*. "The Microbiota-Gut-Brain Axis". *Physiological Reviews* 99.4 (2019): 1877-2013.

9. Pascale A., *et al*. "Targeting the microbiota in pharmacology of psychiatric disorders". *Pharmacological Research* 157 (2020): 104856.

10. Trzeciak P and Herbet M. "Role of the Intestinal Microbiome, Intestinal Barrier and Psychobiotics in Depression". *Nutrients* 13.3 (2021): 927.

11. Ridaura V and Belkaid Y. "Gut microbiota: the link to your second brain". *Cell* 161.2 (2015): 193-194.

12. Rieder R., *et al*. "Microbes and mental health: A review". *Brain, Behavior, and Immunity* 66 (2017): 9-17.

13. Rutsch A., *et al*. "The Gut-Brain Axis: How Microbiota and Host Inflammasome Influence Brain Physiology and Pathology". *Frontiers in Immunology* 11 (2020): 604179.

14. Shaik L., *et al*. "Gut-Brain Axis and its Neuro-Psychiatric Effects: A Narrative Review". *Cureus* 12.10 (2020): e11131.

15. Ng QX., *et al*. "A Systematic Review of the Role of Prebiotics and Probiotics in Autism Spectrum Disorders". *Medicina (Kaunas)* 55.5 (2019): 129.

16. Kang DW., *et al*. "Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota". *Scientific Reports* 9.1 (2019): 5821.

17. Buchman AS and Bennett DA. "Cognitive frailty". *The Journal of Nutrition, Health and Aging* 17.9 (2013): 738-739.

18. Kesika P., *et al*. "Role of gut-brain axis, gut microbial composition, and probiotic intervention in Alzheimer's disease". *Life Sciences* 264 (2021): 118627.

19. Khouzam HR., *et al*. "Psychoses in late life: evaluation and management of disorders seen in primary care". *Geriatrics* 60.3 (2005): 26-33.

20. Munawar N., *et al*. "Hidden Role of Gut Microbiome Dysbiosis in Schizophrenia: Antipsychotics or Psychobiotics as Therapeutics?" *International Journal of Molecular Sciences* 22 (2021): 7671.

21. Fond GB., *et al*. "Microbiota-Orientated Treatments for Major Depression and Schizophrenia". *Nutrients* 12.4 (2020): 1024.

22. Khouzam HR. "A review of trazodone use in psychiatric and medical conditions". *Postgraduate Medicine* 129.1 (2017): 140-148.

23. Fond GB., *et al*. "Microbiota-Orientated Treatments for Major Depression and Schizophrenia". *Nutrients* 12.4 (2020): 1024.

24. Johnson D., *et al*. "Exploring the Role and Potential of Probiotics in the Field of Mental Health: Major Depressive Disorder". *Nutrients* 13.5 (2021): 1728.

25. Liu RT., *et al*. "Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials". *Neuroscience and Biobehavioral Reviews* 102 (2019): 13-23.

26. Foster JA., *et al*. "Gut-brain axis: how the microbiome influences anxiety and depression". *Trends in Neurosciences* 36.5 (2013): 305-312.

27. Nikolova VL., *et al*. "Perturbations in Gut Microbiota Composition in Psychiatric Disorders: A Review and Meta-analysis". *JAMA Psychiatry* 78.12 (2021): 1343-1354.

28. Maybee J., *et al*. "The Gut-Brain-Microbiome Connection: Can Probiotics Decrease Anxiety and Depression?" *Issues in Mental Health Nursing* 5 (2022): 1-8.

29. Mörkl S., *et al*. "Probiotics and the Microbiota-Gut-Brain Axis: Focus on Psychiatry". *Current Nutrition Reports* 9.3 (2020): 171-182.

30. Khouzam HR. "Posttraumatic stress disorder and aging". *Postgraduate Medicine* 120.3 (2008): 122-129.

31. Tanelian A., *et al*. "Resilience or susceptibility to traumatic stress: Potential influence of the microbiome". *Neurobiology of Stress* 19 (2022): 100461.

32. Liang S., *et al*. "Administration of Lactobacillus helveticus NS8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress". *Neuroscience* 310 (2015): 561-577.

33. Gareau MG. "Microbiota-gut-brain axis and cognitive function". *Advances in Experimental Medicine and Biology* 817 (2014): 357-371.

34. Savignac HM., *et al*. "Bifidobacteria modulate cognitive processes in an anxious mouse strain". *Behavioural Brain Research* 287 (2015): 59-72.

35. Rees JC. "Obsessive-compulsive disorder and gut microbiota dysregulation". *Medical Hypotheses* 82.2 (2014): 163-166.

36. Khouzam HR. "Levetiracetam Treatment of Refractory Obsessive-Compulsive Disorder". *Annals of Psychiatry and Mental Health* 3.6 (2015): 1045.

37. Turna J., *et al*. "What's bugging the gut in ocd?" a review of the gut microbiome in obsessive-compulsive disorder". *Depress Anxiety* 33.3 (2016): 171-178.

38. Domènech L., *et al*. "Changes in the stool and oropharyngeal microbiome in obsessive-compulsive disorder". *Scientific Reports* 12.1 (2022): 1448.

39. Turna J., *et al*. "The gut microbiome and inflammation in obsessive-compulsive disorder patients compared to age- and sex-matched controls: a pilot study". *Acta Psychiatrica Scandinavica* 142.4 (2020): 337-347.

40. Della Vecchia A and Marazziti D. "Back to the Future: The Role of Infections in Psychopathology. Focus on OCD". *Clinical Neuropsychiatry* 19.4 (2022): 248-263.

41. John GK and Mullin GE. "The Gut Microbiome and Obesity". *Current Oncology Reports* 18.7 (2016): 45.

42. Butler MJ., *et al*. "The Role of the Gut Microbiome, Immunity, and Neuroinflammation in the Pathophysiology of Eating Disorders". *Nutrients* 13.2 (2021): 500.

43. Carbone EA., *et al*. "A systematic review on the role of microbiota in the pathogenesis and treatment of eating disorders". *European Psychiatry* 64.1 (2020): e2.

44. Russell JT., *et al*. "The Gut Microbiome and Substance Use Disorder". *Frontiers in Neuroscience* 15 (2021): 725500.

45. Jerlhag E. "Gut-brain axis and addictive disorders: A review with focus on alcohol and drugs of abuse". *Pharmacology and Therapeutics* 196 (2019): 1-14.

46. Meckel KR and Kiraly DD. "A potential role for the gut microbiome in substance use disorders". *Psychopharmacology (Berl)* 236.5 (2019): 1513-1530.