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The Emerging Role of the Gut Microbiome in Posttraumatic Stress Disorder

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Abstract

Posttraumatic stress disorder (PTSD) occurs in some people following exposure to a terrifying or catastrophic event involving actual/threatened death, serious injury, or sexual violence. PTSD is a common and debilitating mental disorder that imposes a significant burden on individuals, their families, health services, and society. Moreover, PTSD is a risk factor for chronic diseases such as coronary heart disease, stroke, diabetes, as well as premature mortality. Furthermore, PTSD is associated with dysregulated immune function. Despite the high prevalence of PTSD, the mechanisms underlying its etiology and manifestations remain poorly understood. Compelling evidence indicates that the human gut microbiome, a complex community of microorganisms living in the gastrointestinal tract, plays a crucial role in the development and function of the host nervous system, complex behaviors, and brain circuits. The gut microbiome may contribute to PTSD by influencing inflammation, stress responses, and neurotransmitter signaling, while bidirectional communication between the gut and brain involves mechanisms such as microbial metabolites, immune system activation, and the vagus nerve. In this literature review, we summarize recent findings on the role of the gut microbiome in PTSD in both human and animal studies. We discuss the methodological limitations of existing studies and suggest future research directions to further understand the role of the gut microbiome in PTSD.

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Contributions

Y.-Y.L. and K.C.K. conceived and designed the project. S.K., Y.-Y.L., and K.C.K. prepared the manuscript. J.H. and K.J.R. reviewed and edited the manuscript. All authors approved the manuscript.

Declaration of interests

The authors declare no competing interests.

Keywords

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Introduction

Posttraumatic stress disorder (PTSD) is a common and debilitating mental disorder that occurs in some persons after exposure to a traumatic event, such as physical or sexual violence, combat, or a severe accident. The cross-national lifetime prevalence of PTSD among countries (n=24) participating in the World Health Organization World Mental Health Surveys was 3.9%[1]. The prevalence of PTSD is higher in countries with a recent history of collective trauma (such as war and conflict) as well as in groups with higher rates of trauma exposure. In Africa, for instance, a systematic review found that current PTSD prevalence ranged from 8% in conflict unexposed regions to 30% in high conflict regions[2]. Moreover, PTSD is a significant risk factor for chronic diseases such as diabetes[3], coronary heart disease[4,5], stroke[6], cardiometabolic disease[7], autoimmune diseases[8], and is associated with cognitive decline[9] and early mortality[10]. Thus, comprehending the pathophysiology of PTSD is critical for us to understand risk and resilience following trauma, as well as to identify the mechanisms underlying the relationship between PTSD and chronic diseases.

Although substantial research has greatly improved our knowledge regarding the prevalence, clinical symptoms, and consequences of PTSD over the last decades, much remains to be learned regarding why some persons are more vulnerable to developing PTSD after trauma and the mechanisms driving the relationship between PTSD and chronic diseases. Notably, one area that has been understudied is the relationship between PTSD and the gut microbiome. The human body is home to trillions of microbes, especially the gastrointestinal (GI) tract. Those microbes, together with their genomes, are collectively known as the human microbiome[11]. Rather than simple passengers in or on our bodies, commensal microbes play critical roles in physical health, immune function, inflammation, and in disease[12]. A disrupted gut microbiome has been associated with brain function and various psychiatric disorders[13]. The ‘microbiota–gut–brain axis’ refers to the complex connections involving multiple biological systems that allow bidirectional communication between gut microbes and the brain (Figure 1). For example, psychological factors such as stress or depression may modulate the composition and activity of the gut microbial community through the limbic system (e.g., amygdala, hippocampus, fornix, thalamus, septum, and prefrontal cortex) to release stress hormones (e.g., noradrenaline)[14]. And the gut microbiota can influence brain activity and behavior through various pathways, including microbial products (e.g., gamma-aminobutyric acid, short-chain fatty acids (SCFA), and serotonin precursors) entering the brain via the bloodstream, cytokine release from mucosal immune cells, the release of gut hormones like serotonin from enteroendocrine cells, and afferent neural pathways, such as the vagus nerve. It is crucial to maintaining homeostasis of the gastrointestinal, central nervous, and microbial systems of the host[15]. The potential role of the gut microbiome in mental health and a range of chronic diseases is increasingly recognized[16,17]. For example, the human gut microbiome has been proposed to be involved in the interaction between inflammation and stress regulation in the brain through the

cytokines and other inflammatory signaling molecules[13]. However, the role of the human microbiome in PTSD specifically has yet to be understood.

The hypothalamic-pituitary-adrenal (HPA) axis is the central coordinator of how humans respond to stressful situations, and PTSD is often associated with alterations in the HPA axis[18]. Furthermore, the HPA axis affects both immune and inflammatory responses (e.g., cortisol is a primary suppressor of inflammation), and inflammatory cytokines can activate the HPA system. Recent accumulating evidence indicates that the gut microbiome can affect the development and regulation of the HPA axis and thus affect the neuroendocrine system in the brain[19]. Hence, one direct mechanism by which the gut microbiome may play an important role in the development and progression of PTSD is via its interaction with the HPA neuroendocrine stress axis.

Currently, there are a few review studies on this field. For example, Leclercq *et al.* suggested that the gut microbiome may be key in determining an individual's susceptibility to developing PTSD after a traumatic event[20]. Brenner *et al.* conducted a systematic review to evaluate existing studies on prebiotic and probiotic interventions for traumatic brain injury and PTSD patients[21]. Malan-Muller *et al.* undertook a review study that highlights emerging microbiome research in psychiatric disorders, with a specific emphasis on anxiety- and trauma-related disorders, and explores the gut microbiome as a potential therapeutic target[22]. In another study, the effects of trauma on the gut microbiome, the influence of the gut microbiome on brain function, and the role of the bidirectional Microbiota-Gut-Brain axis in determining individual resilience or vulnerability to PTSD development after trauma exposure were summarized[23]. Here we review the latest existing studies on the PTSD–microbiome association and interventional studies that examined the effect of microbiome-targeted supplementation on PTSD. We further explore the notion that the gut microbiome may play an important role in mediating symptoms of PTSD. We also point out both encouraging findings and methodological limitations in those studies, and we suggest future directions for systematically investigating the role of the gut microbiome in PTSD.

The Microbiota-Gut-Brain Axis.

A growing body of basic science indicates the presence of a 'microbiota-gut-brain axis' linking gut microbiota and mental health[24,25]. A bidirectional communication between the brain, gut, and gut microbiome acts via various routes including nervous, endocrine, and immune signaling pathways[26]. From the 'top down', via the central nervous system, acute stress can alter the composition and function of the gut microbiome, the control of gastrointestinal motility, permeability, and the release of luminal neurotransmitters[27]. From the 'bottom up', rodent models have shown that the gut microbiome influences stress-related neurocircuitry and behaviors, feeding behavior, and obesity through neuro-immune-neuroendocrine pathways[24,26,28–35], and the gut microbiome can regulate neuronal function and fear extinction learning[36]. Clinical studies also suggest a key role of the gut microbiome in depression[37,38]. Moreover, clinical studies using prebiotics (microbiota-targeting diets)[39,40], as well as probiotics (bacterial strains)[41–47], have shown promise to reduce stress, improve cognitive function, and/or alleviate depressive symptoms. With regard to PTSD specifically, previous human correlational studies and animal experiments

suggest a brain-gut connection[48–65], whereby gut microbiota influences both amygdala development and response[66]. Neuroimaging studies demonstrate dysregulation in brain circuits involved in learned fear, with an emphasis on the amygdala, which plays a central role in PTSD[67–71]. Despite these important observations, they remain primarily correlational, and the mechanisms by which the gut-brain axis directly affects the neural circuitry of fear and stress circuitry remain largely unknown.

Immune system, microbiome, and PTSD.

The human immune system is a sophisticated network comprising both innate and adaptive components, serving as a critical defense mechanism against external threats and internal disruptions to maintain homeostasis[72]. The microbiome plays an important role in training the host immune system and modulating inflammation, while reciprocally, the immune system shapes the composition and activity of the microbiome[73]. Accumulating evidence highlights the involvement of both innate and adaptive immune systems in the pathophysiology of PTSD[74–76]. Previous evidence indicates that PTSD is connected with the immune system through multiple inflammatory markers, including C-reactive protein, interferon-gamma, interleukin-6, interleukin-10, and tumor necrosis factor-alpha[77–79]. Importantly, the gut microbiome plays a key role in host inflammation. For example, several gut bacterial genera (e.g., *Roseburia* and *Odoribacter*) have been reported to possess potential anti-inflammatory properties through producing some metabolites such as SCFA[80,81]. Therefore, exploring the intricate interplay between the immune system and the gut microbiome in the context of PTSD is of significant importance to unravel the underlying mechanisms of this disorder.

Existing human studies examining the role of the gut microbiome in PTSD.

Epidemiologic studies have found that PTSD is associated with an increased likelihood of developing gastrointestinal disorders[82–84], such as inflammatory bowel disease (IBD)[85]. Indeed, previous studies have shown that patients with IBD are more susceptible to PTSD, and PTSD exacerbates IBD symptoms[86–88]. It is widely recognized that dysbiosis of the human gut microbiome is associated with various inflammation-related health conditions also associated with PTSD, such as IBD[89,90], cardiometabolic disease[91,92], and diabetes[93]. Given these findings, the potential bidirectional effects between the gut microbiome and the stress and immune systems, and extant evidence from animal[94–97] and human studies showing gut dysbiosis associated with depression and anxiety[98–100], the potential role of the gut microbiome in PTSD warrants further attention. In fact, a recent meta-analysis of the microbiome and psychiatric disorders was unable to evaluate the PTSD–microbiome relation specifically because of the paucity of studies directly examining the microbiome in patients with PTSD[38].

To date, only a limited number of observational human studies have examined the PTSD-microbiome association[34,101–103]. The detailed information and key findings of these studies are summarized in Table 1. The first exploratory study[101] (n=30), in a South African cohort, found that three specific phyla (Actinobacteria, Lentisphaerae, and Verrucomicrobia) were able to distinguish individuals with PTSD (n=18) from those who were trauma-exposed

but did not have a PTSD diagnosis (n=12). This study also found that a lower total relative abundance of these phyla correlated with higher PTSD symptoms. The second study[34] (n=93), in a combat-exposed male cirrhotic veteran cohort, found that individuals with combat-related PTSD had decreased levels of microbial diversity and commensal taxa from Lachnospiraceaeae and Ruminococcaceae, and increased levels of pathobionts (e.g., *Enterococcus* and *Escherichia/Shigella*) compared with non-PTSD combat-exposed patients. The third study[102], also in a South African cohort, compared PTSD cases (n=79) to trauma-exposed controls (n=58) and identified a group of periodontal disease-related genera (i.e., *Mitsuokella*, *Odoribacter*, *Catenibacterium*, and *Olsenella*), which could distinguish PTSD from trauma-exposed controls with an accuracy of 66.4%. The relative abundance of this consortium of genera was positively correlated with PTSD severity and childhood trauma. In addition, one study (n=189) conducted on a unique cohort of Israeli veterans who participated in the 1982 Lebanon war reported the associations between the oral microbiota and PTSD[103]. The study found that the specific microbial signatures, especially the abundance of the bacteria *sp_HMT_914, 332* and *871* and *Noxia*) were associated with PTSD severity, as indicated by symptoms such as intrusiveness, arousal, reactivity, anxiety, hostility, memory difficulties, and idiopathic pain. In a recent study (n=148)[104], PTSD was reliably identified using the microbiome profile. The authors found that the genera *Dialister* and *Veillonella* were negatively and positively correlated with PTSD, respectively. Moreover, they transplanted the fecal samples from trauma-exposed adolescents (PTSD vs. No PTSD) into germ-free mice. Fecal microbiota transplantation of trauma-exposed youth with PTSD led to increased neophobia behavior (assessed in the elevated plus maze) in germ-free mice. This result implies that the gut microbiome may play a role in the stress- and anxiety-related symptoms seen in PTSD pathology.

In addition, two interventional studies examined the effect of microbiome-targeted supplementation on PTSD symptoms in combat veterans[105,106]. The first study[105], conducted on 10 combat veterans with PTSD, found that regular consumption of fermented soy formulation (FSWW08) for a period of 6 months led to a reduction in anxiety, derealization/detachment, general infection, headache, loss of appetite, panic, upper gastrointestinal burning, and upper respiratory infection. However, causal inference from this study is limited by the lack of a control group as well as the small sample size, selection factors, and reporting biases. In the second study[106] involving 31 combat veterans with PTSD, participants were randomized to either an intervention group receiving *Lactobacillus reuteri* DSM 17938 supplementation or a placebo group (daily for 8 weeks +/− 2 weeks) at a 1:1 ratio, stratified by irritable bowel syndrome status. Probiotic supplementation showed a trend towards a decrease in plasma C-reactive protein (CRP) concentrations compared to the placebo group, and although no significant between-group differences were observed in stress responsivity during the Trier Social Stress Test post-supplementation, the placebo group exhibited a significantly larger increase in mean heart beats per minute between baseline and the math task compared to the probiotic group.

Current Barriers to Progress.

The progress in the field of the PTSD gut microbiome has been constrained by several methodological limitations: (1) Reliance on small and clinically ascertained samples. (2)

Risk of confounding bias, such that the relation between PTSD and the microbiome may be explained by a third host factor (e.g., IBD, socioeconomic status, diet, or depression). (3) Failure to distinguish the effects of trauma vs. PTSD in some studies. (4) Using only 16S rRNA gene sequencing, which only offers taxonomic profiles with low resolution (e.g., family and genus levels) and does not offer functional profiles of the gut microbiome. (5) Lack of causal analysis and rational design of microbiota-targeted interventions. (6) The only U.S.-based microbiome studies in PTSD have been conducted in male veterans; the other large microbiome initiatives are all male veteran-focused. Notably, PTSD is more common among women than men[107], and civilians differ from veterans on many important characteristics important for health[108]. Thus, larger and more well-controlled samples, as well as studies on women and civilians, are needed. An additional common limitation of these studies is, with one exception, the lack of integration of insights from animal experiments to test whether microbiome-targeted interventions can alter stress-induced behavior related to neural circuits implicated in PTSD. Such translational studies are necessary to understand mechanisms and to demonstrate causality.

Animal models used in studying PTSD.

Animal models have been extensively utilized to study the role of the gut microbiome in various brain disorders, e.g., autism[50–52,55,56], Parkinson's Disease[48,49,62], and Alzheimer's Disease[53,54]. Although PTSD is a complex heterogeneous phenotype that is difficult to model in animals[109–111], animal studies remain a critical tool for advancing our understanding of PTSD and the neurobiology of stress[112–114]. In fact, animal models are useful complements to human studies to investigate causal relations where such human studies are neither ethical nor feasible. We simply cannot randomly assign humans to trauma exposure and assess their gut microbiome before and after trauma. Moreover, rodents have demonstrated biologically preserved behavioral and neurobiological responses to stress, which further underlie the use of rodent models in studying the threat- and stress-related neurocircuitry relevant to PTSD[115,116].

Note that there are no animal models of PTSD, but animal models that address neurobiological questions relevant to PTSD do exist. In particular, given that PTSD results from stressful, traumatic experiences, rodent models can simulate stress induction (by applying physical, social, and psychological stressors individually or in combination) and certain aspects of disorder development, in particular those focused on the neural circuitry of threat-related behaviors[117]. Thus, animal models are an indispensable tool to investigate underlying neurocircuitry and pathways and, in particular, the complex interaction of environmental, genetic, neuroendocrine, and gut microbiome factors that may contribute to the development of PTSD.

Currently, multiple stress paradigms, including physical stressors (e.g., footshock, restraint/immobilization stress, underwater stress, and single prolonged stress), social stressors (e.g., housing instability, early life stress, and social defeat), and psychological stressors (e.g., predator and predator odor) represent some of the most etiologically relevant approaches in preclinical research[109,110,112,113,115,116,118–121]. The different stressors can lead to different behavioral changes in animals. Each model has its advantages and disadvantages, and it

can address a different neurobiological question. There is no single model that serves all purposes effectively.

Given the fact that only some people exposed to stress ultimately develop PTSD[122], understanding of mechanisms of susceptibility and resilience is important for understanding the pathophysiology of PTSD. Therefore, it is essential to develop an animal model capable of discerning the factors that contribute to susceptibility or resilience to PTSD. This model is important for understanding the mechanisms that determine the individual variability in the development of PTSD.

Existing rodent studies examining the role of the gut microbiome in the neurocircuits of PTSD.

The role of the microbiome in neurocircuits implicated in PTSD has been investigated in animal studies (Table 2). For example, there are several animal studies that investigated the relationship between the gut microbiome and such neurocircuits using a social defeat stress model. Gautam *et al.*[33] investigated how the gut microbiome of male mice responded to exposure to aggressor mice using a cage-within-cage resident-intruder all-male model. They found that the genus *Oscillospira*, *Lactobacillus*, *Akkermansia*, and *Anaeroplasma* are the top differential abundant genera between control and stressor-exposed mice. Similarly, Hoke *et al.*[123] reported that the exposure to aggressor-exposed social stress caused a notable shift in the time-resolved ratios of Firmicutes and Bacteroidetes and an alternation in the relative abundances of Verrucomicrobia and Actinobacteria. Pearson-Leary *et al.*[124] demonstrated that immune-modulating microbiota, such as *Clostridia*, were upregulated in short-defeat latencies rats compared to long-defeat latencies rats or control rats. Specifically, they transplanted fecal samples from the three groups to naïve and non-stressed recipient rats via oral gavage and found that fecal transplants from short-defeat latencies/vulnerable rats to naive, non-stressed rats can decrease the latency to immobility and increase the time of mouse spent immobile in the forced swim test. Using a chronic subordinate colony housing (CSC) stress paradigm, Reber et al. showed that the administration of a heat-killed preparation of *Mycobacterium vaccae* can prevent stress-induced pathology[120]. Additionally, their findings indicated that the CSC paradigm led to increased abundance of *Helicobacter*. Langgartner *et al.*[125] demonstrated that transplanting feces from non-stressed single-housed control mice had mild stress-protective effects on mice exposed to a CSC stress paradigm. Specifically, this was evident in the improvement of CSC-induced thymus atrophy, systemic low-grade inflammation, alterations in bone homeostasis, and a decrease in the time spent in the corners during the open-field test.

In a separate molecular approach, Szyszkowicz *et al.*[126] indicated that changes in mRNA expression of interleukin (IL)-1β and IL-6 within the prefrontal cortex were correlated with the abundance of *Flavobacterium* spp. and *Turicibacter* spp in male C57BL/6 mice previously exposed to chronic social defeat stress (CSDS). Furthermore, these bacterial species were highly associated with social avoidance severity in a social interaction test. Yang *et al.*[127] demonstrated that *Bifidobacterium* might benefit CSDS-exposed mice as it significantly increases the time mouse spent in the interaction zone during a social

interaction test compared with the vehicle group. Interestingly, another study reported that the treatment with *Lactobacillus rhamnosus* decreased CSDS-induced anxiety-like behavior and prevented deficits in social interaction with conspecifics[128]. Bastiaanssen *et al.*[129] demonstrated that the volatility (the degree of compositional change over time) of the microbiome was significantly associated with the social interaction ratio and corticosterone responses in male mice using a chronic psychosocial stress paradigm. In addition, Laudani *et al.*[130] found that 24-hour restraint stress significantly affected the microbial structure in mice with long-lasting hyperarousal. Also, the mice with ephemeral hyperarousal displayed reduced volatility after restraint stress exposure compared to long-lasting hyperarousal mice. In a different stress paradigm (i.e., single prolonged stress: SPS, consisting of 2 hours restraint stress followed by 20 min forced swim stress and subsequent ether exposure), researchers observed various SPS-induced changes in the gut microbiome of male Sprague-Dawley rats[131,132]. In a recent study using SPS[133], differences in the gut microbial composition, functionality, and metabolites were observed in outbred female rats before and after trauma, and these differences correlated with their coping abilities in response to traumatic stress experiences.

With a different type of stress approach - a rat model of trauma and hemorrhagic shock coupled with either 0, 7, or 14 days of restraint cylinder stress - a previous study suggests that persistent stress may be a driving factor associated with the continued changes in microbial diversity after trauma[134]. Moreover, a recent study demonstrated that several microbial species (e.g., *Akkermansia muciniphila* and *Parabacteroides distasonis*) were significantly enriched in mice behaving similarly to non-stressed mice when compared to the mice that showed extreme responses after foot shock stress[135]. However, no consistent overall picture of the microbiome has yet emerged from these animal studies.

Although animal models offer an opportunity to understand the interaction between the microbiome and neurocircuits implicated in PTSD, several challenges remain. And despite that animal studies are a key step to address neurobiological questions relevant to PTSD, animal models cannot replicate human illness. Additionally, experimental protocols in animal studies are often not standardized, complicating inter-study comparison and validation of findings. Moreover, differences in animal (e.g., age, sex, species/strain, and vendor), housing conditions (e.g., co-housing and individually ventilated cages), incubation time (i.e., the period between stress stimuli and testing), acclimation time (to the testing room), specific behavioral tests conducted and their order, etc., further aggravate the problem of variability across animal studies. Recent advances in sequencing techniques and computational tools have allowed an increasing number of metagenomics studies to be performed. However, the analysis of the microbiome can be affected by multiple factors, including sample collection (e.g., collection tubes containing preservative media or not containing preservative media), sample transportation (e.g., ice pack, liquid nitrogen, and collection tubes containing preservative media), DNA extraction (e.g., sample volume, preprocessing, and DNA collection kit), genome sequencing (e.g., sequencing platform, sequencing depth, sequencing errors, and genomic repeats), and cumbersome downstream analysis (e.g. quality control and statistical analyses), etc. Together, these factors have significant effects on results, their consistency and reproducibility, highlighting the need to establish a uniform experimental protocol.

Sex differences in understanding the interactions between the microbiome and PTSD.

As we mentioned above, PTSD is more prevalent in women than men[107]. Previous studies in humans and animal models suggested that differences between the way that the gonadal hormones testosterone or estrogen interact with the HPA axis or modulate hippocampal functioning may contribute to this[112,136–139]. In particular, the expression of pathological symptoms of PTSD in females may vary from those observed in males[140]. Sex is also one of the important host factors affecting the human microbiome[141,142] and animal microbiome[143,144]. Sex-related differences, such as sex hormones, may interact with the gut microbiome, potentially influencing the gut-brain axis and contributing to the development of PTSD. Further research is needed to understand the effects of sex differences on PTSD in both human and animal studies.

Potential Future Directions.

To address the limitations identified above and enhance the scientific rigor of studies in this field, we suggest the following directions for future research: (1) leveraging large human cohorts (especially community dwelling civilian women) with both gut microbiome and PTSD data, as well as numerous potential host factors including demographic, socioeconomic, and health variables available; (2) prospective assessment of trauma/PTSD prior to microbiome sample collection in human cohorts to examine whether PTSD is related to the microbiome over and above trauma exposure alone; (3) using whole-metagenome shotgun (WMS) sequencing data that offers both taxonomic and functional profiles of the gut microbiome; (4) integrating multi-omics data (metagenomics, metatranscriptomic, and metabolomics) to systematically understand the mechanisms linking the intestine and PTSD as previous studies revealed that abnormal intestinal environment (e.g., intestinal barrier dysfunction, concentration of short-chain fatty acids (SCFA), and various microbial metabolites)[145,146] is associated with PTSD. (4) improving causal inference using novel computational/statistical methods to identify putative PTSD-causal species/pathways, which will help us rationally design synbiotics (the combination of specific probiotics and prebiotics) that may prevent or ameliorate PTSD; and (5) incorporating a combination of uniform and diverse animal models to investigate the causation between stress-related alterations in behavior and gut microbiome.

We expect that the directions proposed above will have three direct and meaningful implications for future research and practice. **First**, they would represent an important advance by providing information on whether PTSD (versus trauma alone) is associated with gut microbiome differences, with careful adjustment for numerous potential host factors. **Second**, emerging evidence suggests that PTSD is associated with immune and inflammatory dysfunction, a range of chronic diseases, as well as cognitive deficits all of which have been associated with a disrupted microbiome. The proposed research strategies will provide the foundation for future studies examining whether PTSD-associated gut microbiome dysbiosis is a contributor to chronic diseases. **Third**, clinical trials are expensive and time consuming and there is limited evidence to support prebiotic or probiotic

supplementation trials for PTSD. Using an animal model with an intervention design can help us disentangle the causal relationships. Overall, the proposed research strategies hold the potential to fundamentally alter our understanding of the biological basis of PTSD and trigger future studies on microbiota-targeted interventions for preventing or mitigating PTSD.

Concluding Remarks

Conducting research on the microbiome and PTSD benefits from collaboration among multidisciplinary research teams with complementary expertise in trauma and PTSD epidemiology, microbiome data analysis, animal models, and clinical microbiology. Given the early stage of this field, there are many opportunities for early career researchers to contribute to its advance. Moreover, cross-cultural variation in the microbiome makes collaborator with the global community including researchers from low income and other countries less represented in PTSD research as well as indigenous researchers whose communities face a higher burden of PTSD. Findings will point to new avenues for research and treatment regarding both vulnerabilities to developing - and the consequences of having - PTSD, providing a highly cost-effective set of strategies for determining if additional investment in randomized controlled trials and developing microbiome-based therapies for individuals with PTSD is worthwhile regarding disrupting the negative physical health consequences of PTSD.

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Highlights

- PTSD is a common and debilitating mental disorder.
- The human microbiome affects the nervous system, behaviors, and brain circuits.
- A microbiome perspective will aid in understanding the pathogenesis of PTSD.
- Animal models aids microbiome-PTSD study.

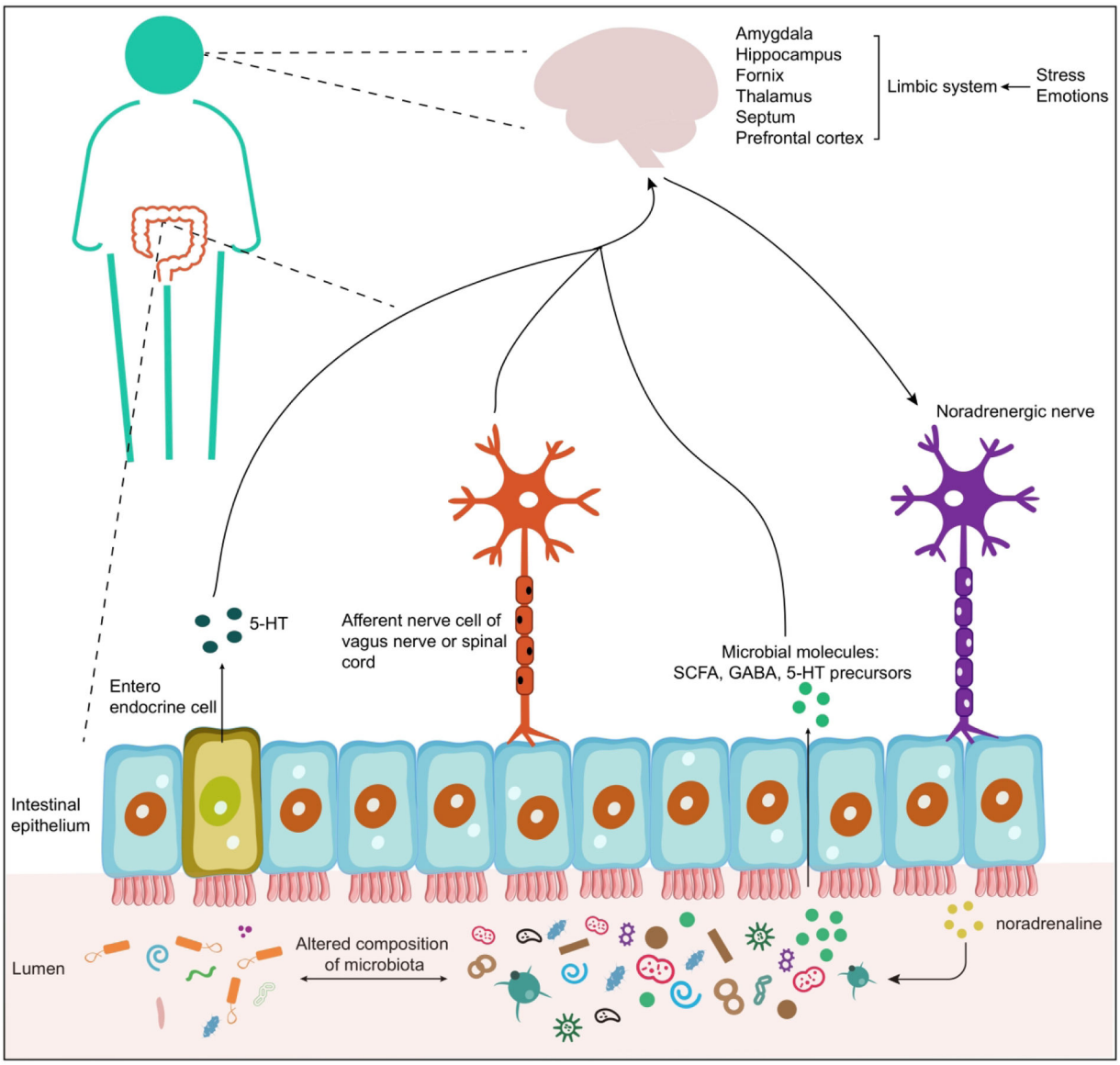

Figure 1: The putative bidirectional communication system of the gut–microbiota–brain axis14.

This system involves the endocrine, humoral, immune, and metabolic pathways. On the one hand, stress and emotions can affect the concentration of stress hormone (e.g., noradrenaline) and neurotransmitters in the gut lumen, and this might contribute to the changes in the composition and activity (e.g., microbial gene expression or signaling between taxa) of the gut microbial community. On the other hand, the microbiota can produce neuroactive compounds such as serotonin [5-hydroxytryptamine (5-HT)], gamma-aminobutyric acid (GABA), and microbial metabolites [short-chain fatty acids (SCFA)]. These metabolites can travel through portal circulation to interact with the host immune system, influence metabolism and/or affect local neuronal cells of the enteric nervous system and afferent pathways of the vagus nerve that signal directly to the brain. Altered composition of microbiota: it pertains to changes in response to stress and alterations in

the microbiota composition, which subsequently influence emotional processing through the bidirectional communication in the gut-brain axis.

Table 1:

Human studies that have identified associations between the human microbiome and PTSD

Study	Population	Sample types	Sequencing platform	Main findings
Hemmings *et al.* (2017)[101]	South African cohort (n=30)	Fecal sample	16S rRNA gene sequencing	Three phyla (Actinobacteria, Lentisphaerae, and Verrucomicrobia) can distinguished those with PTSD from those who were trauma exposed but did not have a PTSD diagnosis.
Bajaj *et al.* (2019)[34]	Combat-exposed male cirrhotic veterans (n=93)	Fecal sample	16S rRNA gene sequencing	Combat-related PTSD is associated with lower microbial diversity, higher pathobionts, and lower autochthonous taxa composition.
Malan-Muller *et al.* (2022)[102]	South African cohort (n=137)	Fecal sample	16S rRNA gene sequencing	The relative abundance of a consortium of four genera (*Mitsuokella*, *Odoribacter*, *Catenibacterium*, and *Olsenella)* was higher in the PTSD group than in the trauma-exposed controls and correlated positively with PTSD severity.
Levert-Levitt *et al.* (2022)[103]	Israeli veterans (n=189)	Saliva sample	16S rRNA gene sequencing	Decreased levels of the bacteria *sp_HMT_914*, *332* and *871* and *Noxia* were correlated with PTSD severity.
Feldman *et al.* (2022)[104]	Mother-child dyads from Sderot, Israel (n=148)	Fecal sample	16S rRNA gene sequencing	The genera *Dialister* and *Veillonella* were negatively and positively correlated with PTSD, respectively. This study provides causative evidence that the microbial trauma profile is at least partially responsible for the trauma-related phenotype.

Table 2:

Animal studies that have identified associations between the microbiome and PTSD

Study	Animal models	Stressor	Sample sizes	Sequencing platform	Main findings
Yang *et al.* (2017)[127]	Male, C57BL/6 mice	Social defeat: male, CD1 aggressor mice	Social defeat: n=14; Control: n=8	16S rRNA gene sequencing	*Bifidobacterium* may benefit chronic social defeat stress exposed mice.
Szyszkowicz et al., (2017)[126]	Male, C57BL/6	Social defeat: male, CD1 aggressor mice	Social defeat: n=18; Control: n=6	16S rRNA gene sequencing	The mRNA expression of interleukin (IL)-1β and IL-6 within the prefrontal cortex were associated with *Flavobacterium* spp. and *Turicibacter* spp., which were also strongly correlated to social interaction ratios using social defeat procedures.
Bharwani et al., (2017)[128]	Male, C57BL/6J mice	Social defeat: male, CD1 aggressor mice	Social defeat: n=32; Control: n33	16S rRNA gene sequencing	The treatment with *Lactobacillus rhamnosus* decreased CSDS-induced anxiety-like behavior and prevented deficits in social interaction with conspecifics
Gautam *et al.* (2018)[33]	Male, C57BL/6J mice	CCRISD: male, SJL albino mice	Agg-E: n=5; Control: n=5	16S rRNA gene sequencing	The genus Oscillospira, *Lactobacillus, Akkermansia* and *Anaeroplasma* were the top four genera that differed between control and stressor-exposed mice.
Pearson-Leary *et al.* (2019)[124]	Male, Long-Evans rats	Social defeat: male Sprague-Dawley rats	Social defeat: n=19; Control: n=8	Shotgun metagenome sequencing	An increased expression of immune-modulating microbiota, such as *Clostridia*, in short-defeat latencies rats was observed.
Zhou *et al.* (2020)[132]	Male, Sprague-Dawley rats	SPS	SPS: n=8; Control: n=8	16S rRNA gene sequencing	Changes in Firmicutes, Bacteroidetes, Cyanobacteria, and Proteobacteria levels were most pronounced after SPS exposure.
Pascual Cuadrado *et al.* (2021)[135]	Male, Arc-CreERT2 x R26-CAGLSL-Sun1-sfGFP-myc mice	FS	FS: n= 33; Control: n=6	16S rRNA gene sequencing	Several microbial taxa (e.g., *Akkermansia muciniphila* and *Parabacteroides distasonis*) were significantly enriched in mice behaving similarly to non-stressed mice when compared to the mice that showed extreme responses after foot shock stress.
Kelly *et al.* (2021)[134]	Male, Sprague-Dawley rats	HS	Control: n=8; LCHS: n=8; LCHS/CS 7/7: n=8; LCHS/CS 14: n=8.	16S rRNA gene sequencing	They identified altered microbiota composition among those groups subjected to chronic restraint stress, then went further to identify a temporal effect over the course of two weeks which improved after removal of stressful stimuli.
Hoke *et al.* (2022)[123]	Male, C57BL/6J mice	CCRISD: male, SJL albino mice	Agg-E: n=5 control: n=5	16S rRNA sequencing	Agg-E SS caused a significant shift in the time-resolved ratios of Firmicutes and Bacteroidetes abundance. Furthermore, Agg-E SS caused diverging shifts in the relative abundances of Verrucomicrobia and Actinobacteria.
Tanelian *et al.* (2022)[131]	Male, Sprague-Dawley outbred rats	SPS	SPS: n=14; Control: n=10	16S rRNA sequencing	After SPS, the gut microbial communities and their predictive functionality shifted especially in SPS cohorts, with volatility at the genus level correlated with the time spent in the center of OF and on the open arms of EPM
Bastiaanssen *et al.* (2022)[129]	Male, C57BL/6J mice	Social defeat: CD1 aggressor mice	Social defeat: n=19; Control: n=41	16S rRNA gene sequencing	The volatility (the degree of compositional change over time) of the microbiome significantly associated with social interaction ratio and corticosterone response.

Study	Animal models	Stressor	Sample sizes	Sequencing platform	Main findings
Laudani *et al.* (2023)[130]	Male, C57BL/6J mice	24-hour restraint	Resilient: n=8; Susceptible: n=9; Control: n=41	16S rRNA gene sequencing	The trauma (24-hour restraint) significantly affected the microbial structure in mice with a long-lasting hyperarousal. And the mice with ephemeral hyperarousal displayed reduced volatility after trauma exposure compared to long-lasting hyperarousal mice.
Tanelian *et al.*, (2023)[133]	Female, female Sprague-Dawley rats	SPS	Stressed: n=16; Control: n=10	16S rRNA gene sequencing	Differences in the gut microbial composition, functionality, and metabolites were observed in outbred female rats before and after trauma.

Agg-E: aggressor-exposed; CCRISD: Cage-within-cage resident intruder social defeat; SD: Social defeat; SPS: Single prolonged stress; HS: Hemorrhagic shock; LCHS: lung contusion with hemorrhagic shock; LCHS/CS 7/7: LCHS plus 7 days of restraint cylinder stress for 2 hours daily; LCHS/CS 14: LCHS plus 14 days of restraint cylinder stress for 2 hours daily; OF: Open Field; EPM: Elevated Plus Maze.