




REVIEW ARTICLE

Human Gastrointestinal Microbiota and Neural Activity: Effects of Probiotics on Mental and GI Health

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Abstract

This review examines the general parameters of the microbiota-gut-brain axis, with special emphasis on a clinical-medical perspective and anthropological research foci. In particular, the authors focused on the observed vs. non-observed (observable) effects of psychobiotics on psychiatric conditions, as well as IBD and IBS comorbidities with psychiatric conditions; the latter was examined within the context of utilizing dietary changes to influence individuals' microbiomes and to ameliorate GI and mental health. Despite some fascinating observations seen in preclinical animal models and promising outcomes observed in several clinical studies of probiotic supplementation on humans with psychiatric as well as GI conditions, this area of research warrants further scientific examination. This research is particularly important in order to provide scientific evidence supporting the use of probiotics (exclusively or as an adjunct treatment) for psychiatric and/or GI conditions in clinical settings. An important consideration in this sense is the need for standardized experimental methods, which can help guide evidence-based recommendations such as differences in dosing, timing, and duration of supplementation, as well as help elucidate genetic predispositions and potential dietary-pharmacological interactions. Such research methods would allow for a better understanding of the processes and mechanisms probiotics induce and/or cause within the context of human physiology.

Method: Scientific literature review and meta-analysis.

Conclusion: Several studies have shown a strong link in terms of causal interaction between mental health and gastrointestinal health. In this regard, mounting evidence from current scientific research warrants the need for incorporating probiotic-rich dietary methods to improve clinical outcomes across a wide range of physical and mental health disorders.

Keywords: Medicine, Neuroscience, Gastrointestinal Health, Mental Health, Probiotics, Human Microbiome

1 | INTRODUCTION

In an effort to provide a more effective therapeutic strategy for a variety of psychological and physical ailments, in recent years the research community has worked on better identifying the connections among multiple body systems. Within this context, the field of microbiota-gut-brain research deserves special recognition. Current medical research has focused on the relationship between the human *microbiome* and several biomarkers such as BDNF, CRP, pro-inflammatory cytokines, as well as neurotransmitters associated with variations in mood and affect such as serotonin Breit et al. (2018) ; Kelly et al. (2015) . In this respect, it is important to underscore how many subjects with assorted psychiatric ailments, especially in comorbidity with gastrointestinal (GI) conditions, report perceived shifts in symptom manifestations based on dietary choices. While some of these accounts are based on clinical case reports, surveys, and patients' self-reports, mounting evidence in laboratory settings is helping the scientific community shed light on the intercommunication among the vagus nerve, brain, and gut Breit et al. (2018) . Therefore, from an evidence-based standpoint, it not unreasonable to assume that the presence of and/or imbalance of different gut microorganisms could contribute to patients' therapeutic outcomes in the aforementioned clinical presentations.

2 | DISCUSSION

Probiotics can be conceptualized as living microorganisms that, when consumed, grant *positive impacts* on the population Huang et al. (2017) . From a statistical standpoint, an increase in general use of the term "psychobiotics" has been observed, to describe the possible useful impacts of probiotics on psychiatric issues Liu et al. (2018) . Multiple studies have been conducted examining the impact of probiotics on mood, both in healthy and clinically affected populations Dickerson et al. (2018) ; Huang et al. (2017) ; Liu et al. (2018) ; Marotta et al. (2019) . These studies have shown conflicting results regarding the efficacy of probiotics on psychiatric conditions. For

example, Huang et al. (2017) did a meta-analysis of published RCTs examining the impact of probiotic supplementation on anxiety. These researchers found that overall, probiotics lowered scores as evidenced on the Depression Anxiety and Stress Scale (DASS), but did not have significant effects when other types of measurements were considered Huang et al. (2017) . They acknowledged that there was quite a bit of heterogeneity among included RCTs and that this served as a limitation in terms of results interpretation Huang et al. (2017).

Additionally, as pointed out by Liu et al. (2018) , who performed a meta-analysis of published RCTs focused on the same subject as Huang et al. (2017) albeit with a larger sample size, Huang et al. (2017) use of the DASS could have notably impacted or even skewed their observed results due to the DASS's measuring of several variables, including anxiety, depression, and stress scores. Given the above-mentioned research problems, the scientific process of assessing overarching trends in anxiety symptoms resulting from probiotic use has been difficult, due to the vast variations in anxiety measures used in RCTs included Liu et al. (2018) . Furthermore, it is important to note that Liu et al. (2018) found no significant differences between probiotic and placebo groups in terms of anxiety symptom relief. They also acknowledged heterogeneity and a paucity of details surrounding important possible moderators on the anxiety-ameliorating impacts of probiotics, such as demographics and particular nuances relating to the different types of probiotics utilized among studies investigated, which could lower the reliability of their result interpretations Liu et al. (2018) .

To provide another example, Marotta et al. (2019) assessed the impact of a 6-week course of probiotics on reported moods of healthy volunteers vs.

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a control group. Their study indicated a significant enhancement of mood, as expressed in terms of reduction of depressive symptoms and anger in the probiotic group compared to the control group, which remained stable (even) three weeks post-discontinuation of probiotic therapy [Marotta et al. \(2019\)](#). The researchers admitted that limitations such as having a small number of participants in the study and possible between-group variations on some personality measures could limit the extrapolation of the results [Marotta et al. \(2019\)](#). Another study related to probiotic therapy and psychiatric disorders was conducted on people recently released from hospitalization due to mania [Dickerson et al. \(2018\)](#). In this RCT study, patients in the experimental group were given probiotics for a 24-week period as an adjunct treatment to examine the risk for future rehospitalizations [Dickerson et al. \(2018\)](#). The results indicated a 2.5-3 fold decreased risk of rehospitalization in the probiotic group and a decreased amount of time spent in the hospital for those patients who were later rehospitalized, and the impact of the former was more pronounced in patients with higher levels of systemic inflammation initially [Dickerson et al. \(2018\)](#). As in previous examples, the authors acknowledged limitations to the study, more specifically, the fact that patients in the study had varying types of treatment post-hospitalization and that the authors did not directly assess the impact of probiotics on participants' microbiomes [Dickerson et al. \(2018\)](#). Of note, the researchers mentioned that participants tolerated the probiotics well and that the low risk and cost of probiotics could warrant more studies in this area [Dickerson et al. \(2018\)](#).

The studies mentioned above elucidate the underlying assumption that additional high quality studies need to be done in order to recommend psychobiotics as a routine part of psychiatric condition treatment. One area within microbiome research that warrants special consideration is the frequently-observed occurrence of comorbid GI conditions and psychiatric conditions. As pointed out by [Andrew Fullwood and Douglas A. Drossman \(1995\)](#), this is a two-way street, with diagnosed psychiatric patients having increased reported bowel complaints and patients diagnosed with bowel conditions having increased psychiatric difficulties. [Andrew Fullwood and Douglas](#)

[A. Drossman \(1995\)](#) also observed the role of stress in GI conditions, as evidenced in 1) ulcers, which likely exacerbate subjective clinical symptoms when human patients are under stress, as well as 2) animal studies demonstrating shifts in intestinal mucosa resulting from stress. Furthermore, the researchers in the aforementioned study note that various *brain-gut* neurotransmitters such as TRH [Figure 1](#) and serotonin help to communicate viscerally perceived sensations such as pain, and can affect both mood and GI distress.

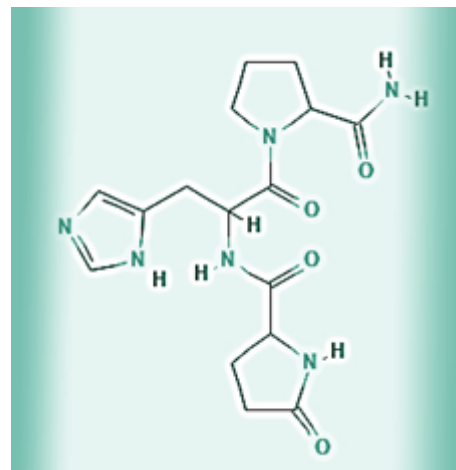


FIGURE 1: Structure of the Thyrotropin-Releasing Hormone (TRH) produced in the hypothalamus. TRH is also defined as Thyrotropin-Releasing Factor (TRF) and presents the following formula: (2S)-N-[(2S)-1-[(2S)-2-carbamoylpyrrolidin-1-yl]-3-(1H-imidazol-5-yl)-1-oxopropan-2-yl]-5-oxopyrrolidin-2-carboxamide.

The authors explain that both psychiatric and GI conditions must be treated for best possible clinical outcomes and also detail specific recommendations for healthcare providers working with patients who have comorbid GI and psychiatric disorders to enhance the therapeutic alliance. As far as recommendations, the study mentions problem-focused coping skills that give patients greater perceived control over their conditions, validating patients' feelings but not encouraging rumination, and setting dialogue boundaries so that the most crucial problem can be prioritized without wasting time for either party member (Fullwood & Drossman, 1995).

The Vagus Nerve represents one of the main methods of communication between the gut and the brain.

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More specifically, as the tenth cranial nerve and primary component of the parasympathetic nervous system [Breit et al. \(2018\)](#), the vagus nerve synapses (among many places) in the gut, to assist with modulation of smooth muscle contraction and the release of digestive chemical substances, in addition to its more crucial afferent functions which include sending messages about inflammation and energy balance to the brain [Breit et al. \(2018\)](#)). The research by [Kelly et al. \(2015\)](#) examines the evidence for a pathway affecting the microbiota-gut-brain relationship that relates to the vagus nerve; its nerve endings can sense when something has gone awry with the intestinal barrier due to factors such as stress, antibiotics, or an unhealthy eating pattern [Figure 2](#).

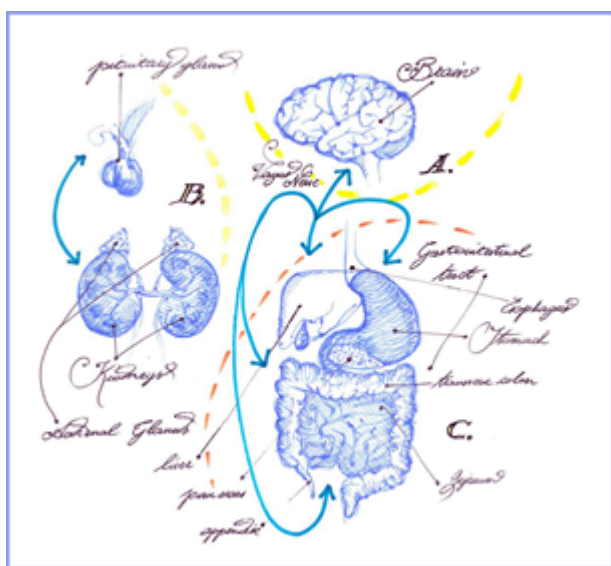


FIGURE 2: A graphic representation of the connections between Central Nervous System (CNS / Brain - A.), Hypothalamic-Pituitary-Adrenal axis (HPA - B.), and Gastrointestinal Tract (GI - C.) as exemplified in the Microbiota-Gut-Brain axis (MGB).

Although more scientific investigations are warranted to provide evidence of a specific mechanism in this context, the so-called “leaky gut” has drastic implications for inflammation in the body and immune responses; the authors in the article above note that deficits in intestinal permeability resulting in inflammation could at least partially help to explain the inflammatory markers often seen in psychiatric conditions like depression, and that

the microbiota components can help to maintain intestinal integrity [Kelly et al. \(2015\)](#). Additionally, [Kelly et al. \(2015\)](#) note not only the importance of serotonin in modulating intestinal permeability, but also the crucial role of gut microbiota in helping to modulate serotonin synthesis and release. In terms of outcomes following probiotic supplementation in humans, [Kelly et al. \(2015\)](#) indicate that intestinal barrier integrity can be increased when there is an underlying GI diseased state and a probiotic regimen is followed; however, the researchers importantly point to the absolute need for an investigation into the parameters determining how dysbiosis plays a role in disease etiology, as opposed to simple hypothesizing based on previous observation.

3 | GENERAL CONSIDERATIONS

Several studies have been published on the problematic relation between poor health outcomes and the Standard American Diet or “SAD.” Of note, this label (often utilized in the USA, and synonymically with Western Pattern Diet or WPD) is in itself a misnomer, as this type of diet specifically addresses the United States of America, not the whole American continent, with a vast diversity in terms of dietary strategies and culinary traditions. Aside from semantic debates, the scientific community is in agreement regarding how SAD is drastically different than the diet human ancestors used to eat thousands of years ago. In recent times, an upsurge in research interest regarding potential health benefits of probiotic-rich foods has been observed, especially as the understanding of the gut microbiome continues to improve [Selhub et al. \(2014\)](#). Furthermore, the topic of nutritional psychiatry has gained considerable traction in recent years, as connections between mental health and diet continue to be investigated through new studies [Müller-Waldeck \(2019\)](#). This area of research is particularly striking because there are massive variations in observed associations between eating patterns and mental health, depending on which geo-cultural area researchers focus on, as well as the specific quantities of a given food or drink being consumed [Selhub et al. \(2014\)](#). For example, alcohol (itself a depressant) consumption has been

linked to depression (intended as a clinical diagnosis, as in MDD), and yet it is not considered a risky problematic factor, if the individual consuming alcohol is drinking it along with (read: “while”) eating a more “traditional” and thus healthier diet [Selhub et al. \(2014\)](#) .

Research has also indicated how certain foods are observed to help defend against depression. In this category we find soy products, turmeric and blueberries [Selhub et al. \(2014\)](#) , all of which are known to have potent anti-inflammatory effects that could help mitigate depressive tendencies. The process of fermentation is known to improve bioavailability of nutrients, which could at least partially explain the positive effects seen as a result of eating probiotic-rich foods [Selhub et al. \(2014\)](#) . The probiotic *Lactobacillus rhamnosus* has been observed to decrease anxiety and depressive-like behaviors in healthy but stressed animals, as evidenced in rodent models such as the elevated plus maze and forced swimming test [Selhub et al. \(2014\)](#) . As in other similar studies, there are shortcomings associated with animal studies and the ability to generalize this data to humans; however, the overall statistical trends providing more robust evidence for this connection is relevant in contemporary clinical efforts. Furthermore, it is possible and even likely from a statistical standpoint [Müller-Waldeck \(2019\)](#) , that the naturally occurring beneficial microorganisms found on raw fruits and vegetables could in part explain the more robust health seen in populations of people eating more traditional diets [Selhub et al. \(2014\)](#) . For example, the Japanese population (especially within the Japanese prefecture of Okinawa / Ryukyu Islands) has been monitored by the scientific community for their higher life-expectancy and overall better health, healthier diet (especially in comparison to SAD), with plenty of fermented items like soy products and vegetables compared to other areas of the world; one study in particular observed that people living in rural Japan possessed more diverse collections of gut microorganisms and larger amounts of both Bifidobacterium and Lactobacilli [Selhub et al. \(2014\)](#) . Moreover, it has been a commonly observed trend that those adhering to more traditional ways of eating tend to have increased microbiota diversity [Selhub et al. \(2014\)](#) .

In juxtaposition to the aforementioned ethno-cultural dietary customs, SAD has been considered *inflammatory* due to its inclusion of significant amounts of high-sugar, minimally nutrient-dense so-called *junk* food [Selhub et al. \(2014\)](#) . These foods are also frequently eaten by subjects with psychiatric conditions [Selhub et al. \(2014\)](#) , which represents yet another layer of complex negative influences on/from environmental health stressors and on/from negative socio-economic status, as observed in multiple areas of investigations and disciplines, for instance –in the context of health and developmental psychology– by Bronfenbrenner (1979) [Bronfenbrenner \(1979\)](#) and [Shelton \(2018\)](#) . Studies have also indicated that foods high in fiber like fermented grains and lentils can aid immune function, decrease inflammation as measured by CRP, and even increase GABA levels [Barengolts \(2016\)](#) ; [Selhub et al. \(2014\)](#) . Beneficial probiotic-rich foods that have been shown to have positive effects on the intestinal microbiome include fermented dairy items like kefir, as well as more traditional dietary components like raw honey, kimchi, miso, and fermented soy [Selhub et al. \(2014\)](#) . It is important to note that although fermented animal foods like meat and fish exist and are commonplace in certain contexts, the potential impacts of these remain less certain [Selhub et al. \(2014\)](#) . Despite the existence of a growing robust body of evidence highlighting the beneficial effects of probiotics on psychiatric and gastrointestinal health, the connection between diet and both gastrointestinal and psychiatric state is still rejected by part of the scientific or medical community especially in the USA, including within the fields of gastroenterology and psychiatry [Bested et al. \(2013\)](#) [Schönemann \(2008\)](#) . At the same time, current research is pointing to more promising potential in terms of connection among microbiota, gut, and mental health. [Zheng et al. \(2016\)](#) explains how people with major depressive disorder (MDD) have significantly different levels of gut microbiome components compared to healthy controls as shown via stool sampling; specifically, the relative amount of Actinobacteria [Figure 3](#) were higher in MDD participants, and the amount of Bacteroidetes was lower, with variations in amounts of Firmicutes as a key distinguishing feature for people with MDD compared to controls.

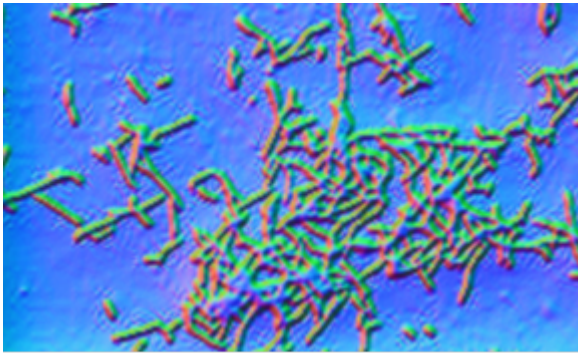


FIGURE 3: Gram-stainlight microscopic (colored) image of Actinobacteria Actinomyces STII.

The authors also highlighted how FMTs from subjects diagnosed with MDD into germ-free mice recipients led to depressive-like behaviors as shown on behavioral tests including the forced swimming test, tail suspension test, and open field test, 2 weeks post-FMT. Both findings suggest that dysbiosis of gut microbiota could have at least a partial impact on depressive behaviors [Zheng et al. \(2016\)](#). A possible follow-up hypothesis reasons that increasing consumption of probiotic-rich foods could enhance quality of life for patients with both GI and psychiatric issues.

4 | CONCLUSION

More studies investigating the links between probiotics and mental and gastrointestinal health are needed. Evidence-based medical research has focused on the psychiatric potential of probiotics given their easy accessibility, relative low risk for side effects, and, from a sociological point of view, (perceived) lack of negative *reputation* [Rauth \(2016\)](#); [Liu et al. \(2018\)](#). In popular knowledge, it is often stated that the “path to health is through the gut,” and in our examination of the research studies at the center of this analysis, there is evidence of a solid intercommunication between the gut microbiome and brain. A more comprehensive examination of such connections is warranted, and the incorporation, in clinical and medical settings, of the knowledge acquired therein. As part of general dietary recommendations, patients should aim to include probiotic-rich foods in their diets under the supervision of

scientific, psychological, and medical professionals. This practice would also suggest possible utilization of high-quality probiotic supplements in addition to mainstream Western medical treatments and other CAM (Complementary and Alternative)-Integrative medical modalities. This approach would of course be weighted against the relative (i.e. by comparison to Western EBM-pharmacopeia counterpart) lack of regulations surrounding supplements in general, which is in part due to cultural and historical components of the way “natural” remedies are perceived as “safe” [Amos et al. \(2014\)](#). Of note, while we could certainly assume that, at least from a statistical point of view, the vast majority of peer-reviewed EBM pharmacological studies are based on solid scientific evidence and have the “patient’s best interest at heart” [Sauerland and Seiler \(2005\)](#), certain claims by CAM-supplement companies which are generally considered unsubstantiated by the scientific community are not ontologically different from similar claims within EBM-Western pharmacy industry. This is for instance noted in –often perceived as *cure-alls*– pharmaceuticals (in popular science publications, e.g. “correcting chemical imbalances” via SSRIs or “eliminating inflammation” via corticosteroids [Lacasse and Leo \(2005\)](#)). Furthermore, while dietary recommendations and the implementation of probiotic-rich foods in the context of CAM should be investigated under the same scientific parameters utilized in medical research in general, the medical community should also pay attention to the patient in their individuality, subjectivity, and experience. This means that, while anecdotal evidence and case reports are usually listed toward the base of the pyramid of *evidence*, this very evidence can no longer be *blind* to the number of investigations published each year, shedding light on both the benefits of gastrointestinal balance through appropriate diet and the benefits of psychobiotics on health in general.

5 | LIMITATIONS AND FUTURE STUDIES

The primary limitations of this study are connected to the reviewing nature of this analysis, due to the clinical safety and exposure parameters for clinical research subjects, following COVID-19 taskforce

recommendations. Future EBM double-blind RCTs and biostatistical-epidemiological analysis are recommended to verify the empirical validity of the results and outcomes discussed herein.

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