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Microbiota, Immunity and Neuroplasticity - The Forgotten Triad of Modern Mental Health

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We live in an era in which mental health disorders have become one of the greatest global public health challenges, with profound implications for the quality of life, productivity and longevity of populations. According to the World Health Organization, more than 970 million people worldwide suffer from some form of mental disorder, with depression and anxiety being the most prevalent. Modern neuroscience has made progress in understanding the neurobiological mechanisms involved in these conditions, but a fundamental component seems to have been neglected for a long time: the interaction between the gut, the immune system and the plasticity of the brain.

Traditionally, mental health has been investigated from the perspective of neurotransmitters, genetics, and brain structure, while aspects such as the composition of the gut microbiota, the regulation of the immune system, and the brain's ability to adapt structurally, functionally, and synaptically have been treated as separate areas. However, recent studies point to a close relationship between these three dimensions. The gut microbiota, composed of trillions of microorganisms that colonize the gastrointestinal tract, interacts dynamically with the central nervous system through immunological, metabolic, and neural pathways. This interaction occurs mainly through the so-called gut-brain axis, which is currently emerging as one of the most promising areas of translational neuropsychiatry.

At the same time, neuroplasticity, understood as the nervous system's ability to reorganize its connections and structures in response to stimuli, experiences or injuries, is strongly modulated by inflammatory and immunological factors. We now know that pro-inflammatory cytokines, such as IL-6, TNF-alpha and IL-1 beta, play a direct role in inhibiting neurogenesis and synaptic plasticity, and are associated with resistant depression, cognitive impairment and neurodegenerative diseases such as Alzheimer's and Parkinson's.

Therefore, integrating knowledge about microbiota, immunity and neuroplasticity into a unified model is not only an interesting scientific proposal, but an urgent clinical need. This triad forms a constant feedback loop, in which imbalances in the microbiota can generate low-grade systemic inflammation, compromising the integrity of the blood-brain barrier and limiting the brain's ability to adapt, which in turn contributes to the perpetuation of psychiatric symptoms.

Throughout this article, we will explore each of these components in depth, always supported by updated scientific evidence, and we will point out therapeutic paths that are emerging from precision biotechnology, microbial modulation and personalized medicine.

The Gut Microbiota as an Orchestrator of Mental Health

The intestinal microbiota, also known as the gut microbiome, is composed of more than 100 trillion microorganisms, including. bacteria, viruses, fungi and archaea, which coexist in balance with the human host. The genetic makeup of these microorganisms exceeds the number of genes in the human genome by more than 150 times, and is considered a functional “organ” with essential metabolic, immunological and neurological functions.

Studies published in journals such as *Nature Reviews Neuroscience* (Cryan et al., 2022) and *Brain , Behavior and Immunity* (Jiang et al., 2015) confirm the relationship between intestinal dysbiosis and several mental disorders, including depression, anxiety, autism and Alzheimer's. The loss of microbial diversity and the increase in pro-inflammatory species generate LPS (lipopolysaccharides), which activate the systemic immune response and alter brain signaling. Below, we present a table with the main bacterial genera associated with positive and negative mental health, based on metagenomic studies:

Bacterial Genus	Association with Mental Health	Scientific Evidence
Lactobacillus spp.	Protector	Reduction in anxiety and ASD
Bifidobacterium spp.	Protector	Increased production of GABA
Alistipes spp.	Potentially harmful	High in depression and stress
Clostridium spp.	Ambiguous	It depends on the species and diet
Enterobacteriaceae	Harmful	Associated with inflammation and cognitive dysfunction

Source: Jiang et al., 2015; Foster & Neufeld , 2013.

In addition, the microbiota acts in the production of neuromodulators such as serotonin, dopamine and GABA. It is estimated that around 90% of the body's serotonin is produced in the intestine, directly influenced by species such as *Escherichia coli* , *Candida* and *Streptococcus* .

Clinical studies show that patients with depression have reduced levels of *Lactobacillus* and *Bifidobacterium* , with an increase in inflammatory species such as *Alistipes* . These bacterial patterns directly influence behavior, as shown in animal and human models.

Immune System and Neuroplasticity: The Underappreciated Intersection

The old idea that the brain was immune to inflammatory processes has been overcome by discoveries that show the direct involvement of the immune system in the regulation of brain plasticity. Inflammatory cytokines such as TNF-α, IL-6 and IL-1β inhibit the expression of BDNF (brain-derived neurotrophic factor), which is essential for synapse formation and neurogenesis.

BDNF (Brain-Derived Neurotrophic Factor) is a key mediator of synaptic plasticity and neurogenesis. It stimulates neuronal survival, axonal growth, and cellular differentiation. Studies show that inflammation significantly reduces BDNF levels in the hippocampus, an area critical for memory and emotional regulation (Felger & Lotrich , 2013). Patients with major depression have significantly lower plasma and brain BDNF levels than healthy controls, and these levels tend to normalize with symptom remission.

Furthermore, microglia , the main resident immune cell of the central nervous system, plays a central role in this process. In their physiological state, microglia act in synaptic pruning, damage surveillance and modulation of the neuronal environment. However, when chronically activated, they begin to release reactive oxygen species, proteases and cytokines, creating an environment hostile to neuroplasticity. This condition, called neuroinflammation, is strongly linked to the pathophysiology of neuropsychiatric diseases.

The graph below shows the comparison between healthy individuals and patients with neuropsychiatric disorders in relation to inflammatory and neurotrophic markers :

Clinical condition	IL-6 (pg / mL)	TNF-α (pg / mL)	BDNF (ng / mL)
Healthy control	1.2 ± 0.5	2.1 ± 0.6	32.4 ± 4.5
resistant depression	4.8 ± 1.3	5.2 ± 1.7	19.6 ± 3.2
Early Alzheimer's	6.5 ± 2.0	6.8 ± 1.4	17.2 ± 2.9
Acute bipolar disorder	5.1 ± 1.1	4.6 ± 1.3	20.8 ± 3.6

These data reinforce the need for therapeutic approaches that are not limited to classical neurotransmission, but that also consider the regulation of the immune environment and the restoration of neuroplasticity. The connection between inflammation and loss of plasticity is not just a theoretical hypothesis, but a clinical reality documented by dozens of clinical trials and observational studies.

In the next section, we will explore the interconnection between the three central elements of this proposal: how the microbiota, by modulating the immune system, exerts a direct and indirect influence on neuroplasticity. And, furthermore, how this can be reversed or enhanced through high-precision biotechnological and dietary strategies.

The Interconnection between Microbiota, Immunity and Neuroplasticity

In recent years, advances in technologies such as next-generation sequencing (NGS), metagenomics and mass spectrometry have revealed a complex network of interactions between the central nervous system, the immune system and the intestinal microbiota. Understanding this interconnection is based on the concept of the microbiota-gut-brain axis, which describes the bidirectional communication between these systems, mediated by neural, humoral, endocrine and immunological pathways.

When analyzing the functional impact of this communication, it becomes clear that the microbiota acts as a conductor orchestrating signals to the brain, through the regulation of intestinal permeability, cytokine modulation, production of bioactive metabolites and neuroendocrine signaling. This symphony, when well regulated, favors. neurobiological balance. However, when there is dysbiosis, this communication is distorted, opening space for neuroinflammation and impairment of brain plasticity.

Among the main mechanisms of this interconnection, the microbiota's ability to induce or suppress systemic inflammatory responses stands out. Studies show that beneficial species, such as *Faecalibacterium prausnitzii* and *Bifidobacterium longum* , are associated with the production of butyrate and other short-chain fatty acids, which act as immunomodulators, reducing the production of pro-inflammatory cytokines and promoting the differentiation of regulatory T lymphocytes (Tregs) (Zhang et al., *Cell Host & Microbe* , 2021)

Short-chain fatty acids (SCFAs), especially butyrate , play remarkable roles at the interface between immunity and neural plasticity. Butyrate is capable of inhibiting histone deacetylase (HDAC), promoting the expression of neurotrophic genes such as BDNF. In addition, it acts as an energy fuel for enterocytes, strengthening the intestinal barrier and preventing bacterial translocation and endotoxins such as lipopolysaccharide (LPS), which would activate systemic inflammatory pathways.

A study conducted by Ochoa- Reparaz et al. (2020) showed that mice with microbiota enriched in butyrate- producing species presented greater hippocampal neurogenesis , lower expression of inflammatory cytokines and better performance in spatial memory tests. These findings are consistent with clinical trials that indicate cognitive and emotional improvement in humans subjected to intestinal modulation with probiotics.

Microbiota Component	Immunological Effect	Neurological Effect
F. prausnitzii	Production of butyrate , anti-inflammatory	Increased BDNF, neurogenesis
Lactobacillus plantarum	Reduction of IL-6 and TNF-α	Increased GABA, reduced anxiety
Bifidobacterium longum	Treg induction , increased IL-10	Cognitive and emotional improvement
A. muciniphila	Regulation of the intestinal barrier	Reduction of permeability and endotoxemia
Pathogenic species (e.g. enterotoxigenic *E. coli*)	Increased IL-1β, LPS ↑	Reduced BDNF, increased microgliosis

Source: Ochoa- Repáraz et al., 2020; Zhang et al., 2021; Foster & Neufeld , 2013.

Another important point in the interconnection of this triad is the influence of microbiota metabolites on HPA (hypothalamic-pituitary-adrenal) axis signaling. In animal models, germ-free animals (without microbiota) demonstrate hyperactivity of the HPA axis, with exacerbated elevation of corticosterone in the face of stressful stimuli. This hormonal imbalance compromises hippocampal neuroplasticity and favors the emergence of depressive symptoms (Sudo et al., 2004).

In addition to SCFAs , there are other molecules produced by the microbiota that directly affect the brain, such as:

· **Indole derivative of tryptophan** , which acts as an agonist of aryl -hydrocarbon receptors in the brain, regulating local inflammation.

· **Lactate** , which can be used as an energy source by the brain during stress.

· **Phenylacetylglutamine** , involved in the modulation of adrenergic activity.

Therapeutic Interventions and Future Perspectives

With the scientific recognition of the deep interconnection between intestinal microbiota, the immune system and neuroplasticity, a fertile field opens up for the development of innovative therapeutic approaches. Such interventions not only aim to treat neurological or psychiatric symptoms in a specific way, but also to restore the systemic balance that supports mental health in a comprehensive and lasting way.

In recent years, well-conducted clinical trials have demonstrated that modulating the microbiota through probiotics, prebiotics , synbiotics, diet, and behavioral strategies can result in measurable neurobiological effects. These effects range from improved mood and cognition to structural changes detectable by neuroimaging, such as increased cortical thickness and improved functional brain connectivity.

Probiotics and Psychobiotics: The Future of Neurointestinal Modulation

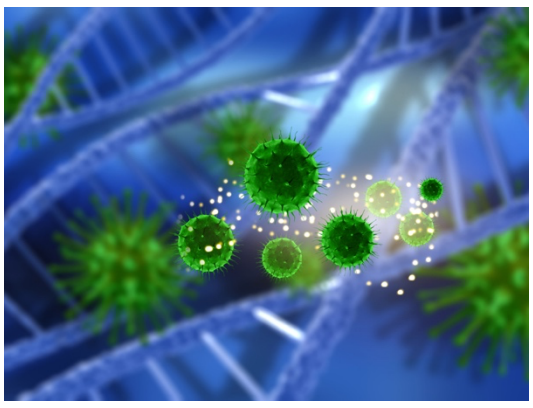
Probiotics are defined by the FAO and the World Health Organization as live microorganisms that, when administered in adequate amounts, confer health benefits on the host. When these benefits are specifically directed at mental health, these probiotics are called **psychobiotics** , a term coined by Dinan et al. (2013) to describe strains with anxiolytic, antidepressant or neuroprotective properties.

Randomized clinical studies with formulations containing *Lactobacillus helveticus* , *Bifidobacterium longum* , *L. rhamnosus* and *L. plantarum* demonstrated significant improvement in symptoms of anxiety and depression in adults and adolescents. In a 2019 study published in the journal *Nutrients* , the authors observed that the administration of *Lactobacillus plantarum 299v* for 8 weeks in college students reduced plasma inflammatory markers, improved sleep quality, and attenuated stress symptoms compared to placebo (Messaoudi et al., 2019).

Furthermore, a trial conducted by Kazemi et al. (2019), involving 110 patients with major depressive disorder, demonstrated that a symbiotic mix containing *L. acidophilus* , *B. bifidum* , *L. I got married* and *FOS* (fructooligosaccharides) significantly reduced depression scores on the Beck scale, in addition to increasing serum BDNF levels.

Prebiotics and Immunomodulatory Nutrients

Prebiotics are substrates selectively used by beneficial microorganisms of the microbiota, which result in positive effects for the host. The most studied are FOS (fructooligosaccharides), GOS (galactooligosaccharides) and inulin, which



increase the concentration of *Bifidobacterium* and *Lactobacillus* in the colon and promote the production of SCFAs such as butyrate and propionate.

Furthermore, specific nutrients have been associated with improved immune response and neuroplastic support . Vitamin D, for example, regulates T-cell differentiation, while magnesium acts as an enzymatic cofactor in BDNF and serotonin pathways. Zinc, selenium, and omega-3 deficiency are also associated with negative mental health outcomes, such as depression, mental fatigue, and cognitive impairment (González et al., 2020).

The future of personalized mental health involves therapies designed based on each individual's microbial, inflammatory and genetic profile. The development of new-generation probiotics, with personalized or genetically optimized strains to produce specific metabolites such as GABA, serotonin or BDNF-like molecules , is already a reality in translational research laboratories.

The use of **fecal, epigenetic and immunological biomarkers** may allow the selection of therapeutic protocols with unprecedented precision, increasing the chances of response and reducing adverse effects. Clinical trials using personalized metagenomics and fecal microbiota transplantation are underway at institutions such as Harvard, Johns Hopkins and Karolinska Institutet , with promising results.

Conclusion

The triad formed by the intestinal microbiota, the immune system and neuroplasticity constitutes a vital axis for the maintenance of human mental health, still underestimated both by conventional clinical practice and by public health policies. The growing recognition of the existence of a microbiota-intestine-brain axis has led to a profound reassessment of the physiological bases that support behavior, cognition and emotional balance, revealing that factors previously considered peripheral – such as diet, subclinical inflammation and intestinal bacterial composition – play a central role in brain regulation.

In this article, we review consistent scientific data demonstrating that the intestinal microbiota directly and indirectly modulates neurotransmitter production, neuroendocrine pathway activity, blood-brain barrier integrity, and systemic immune Response. These effects, in turn, profoundly impact synaptic plasticity, neurogenesis, and the adaptive capacity of the central nervous system. The presence of dysbiosis, chronic low-grade inflammation, and reduction of neuroactive metabolites , such as butyrate , constitute a common pathophysiological scenario in several contemporary neuropsychiatric diseases, including resistant depression, autism spectrum disorders, generalized anxiety disorders, Alzheimer's, and even post-infectious syndromes such as long COVID.

By integrating these three elements – microbiota, immunity and brain plasticity – into a unified model, contemporary science broadens its field of vision beyond the reductionist paradigms of isolated pharmacotherapy. This expanded vision allows not only a more comprehensive explanation of the genesis of mental disorders, but also the basis for safer, more sustainable and more effective therapeutic interventions. Interventions that range from the use of advanced psychobiotics and synbiotics to evidence-based dietary strategies, contemplative practices with neuroimmunological impact and even the development of biointelligent supplements designed based on the individual microbiota profile and expression of neuroinflammatory markers .

There is, therefore, a vast and promising field for the practical application of the accumulated knowledge about this triad. Precision biotechnology, for example, already makes it possible to encapsulate specific microbial strains with the capacity to resist the gastrointestinal tract and release neuroactive metabolites in a controlled manner in the colon. Emerging metagenomics and artificial intelligence technologies will, in the near future, make it possible not only to identify early imbalances in the microbiota, but also to predict the risk of neuropsychiatric disorders based on microbial and immunological signatures. This could transform not only treatment, but the very logic of prevention in mental health.

However, the path to clinical consolidation of this approach still requires overcoming challenges, such as standardizing the strains used, regulating nutraceutical products with functional claims, training medical staff in a more holistic and transdisciplinary vision, and funding robust research that validates large-scale interventions. It is essential that health professionals are aware of the growing scientific evidence and therapeutic possibilities offered by this triad, incorporating the gut-brain axis as a fundamental part of clinical assessment and therapeutic conduct in mental health.

Finally, if we are to truly address the silent epidemic of mental disorders in the 21st century, we will need approaches that understand the human being in all its bioecological complexity, integrating body, mind and microbiota in a constant feedback system. Neglecting this triad is to remain in a fragmented model. Understanding it and intervening in it is to take an evolutionary leap in modern medicine.

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