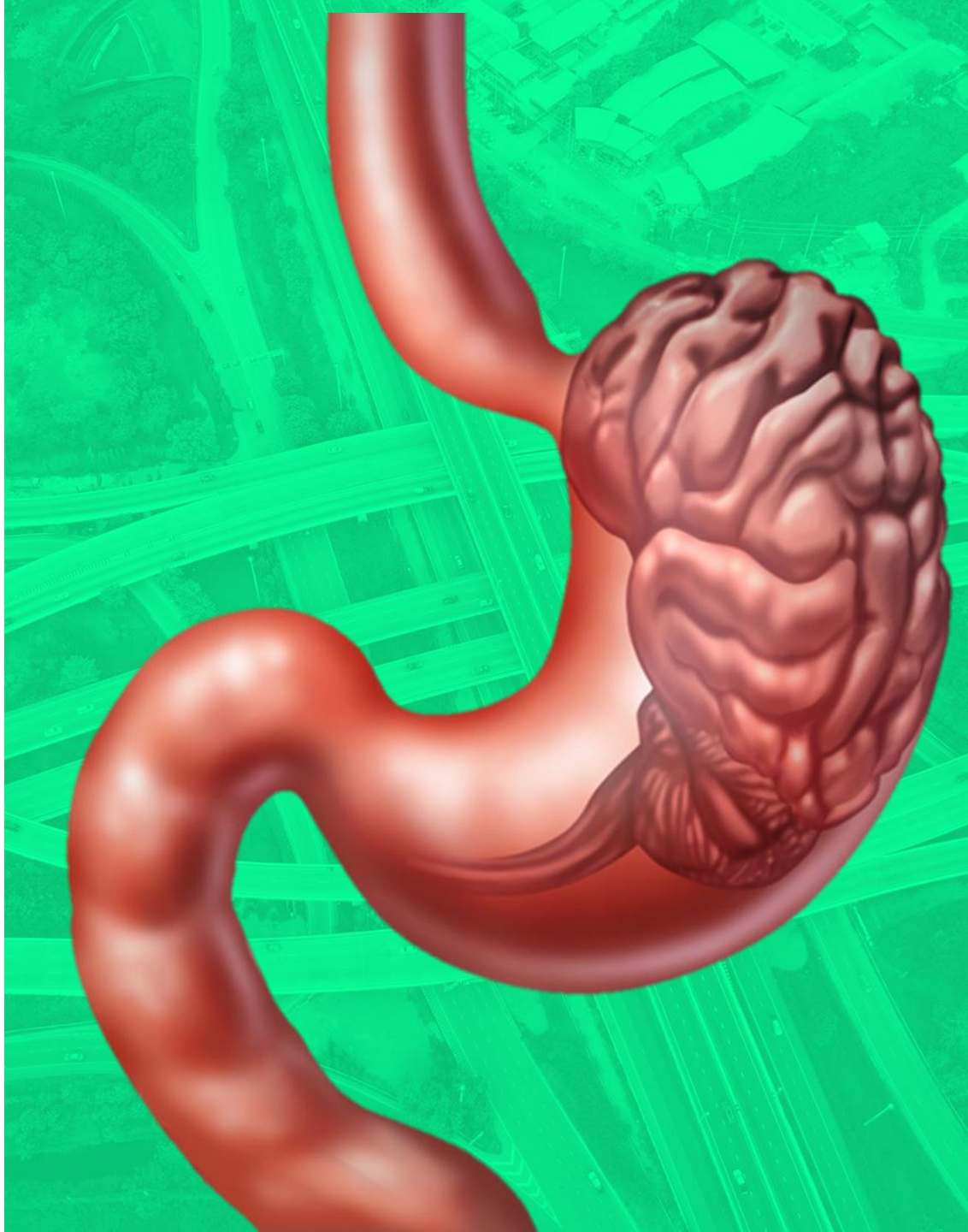
Cerebro e Inflamación:
Diferentes Vías, un Mismo Destino

ORGANIZADO POR

Fundación Lucha contra las Infecciones

ScienHub



20 Febrero 2025

Relevancia clínica del microbioma en el trastorno depresivo

El rol del eje cerebro-intestino-microbiota

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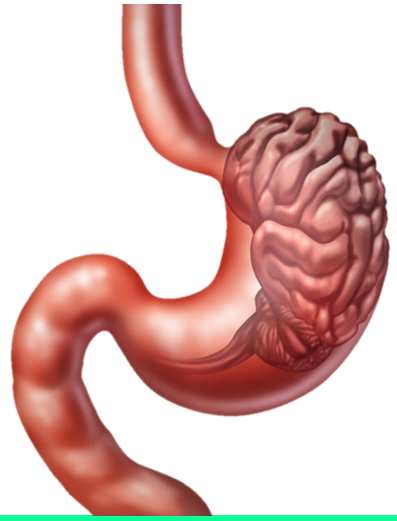
Profesora asociada Facultad de Medicina. Universidad Autónoma de Barcelona.
Investigadora adscrita CIBERSAM (CB15/00154).



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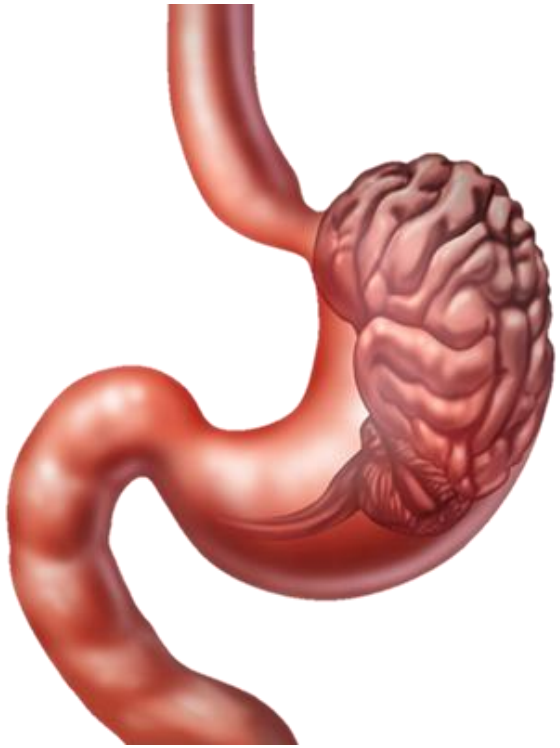
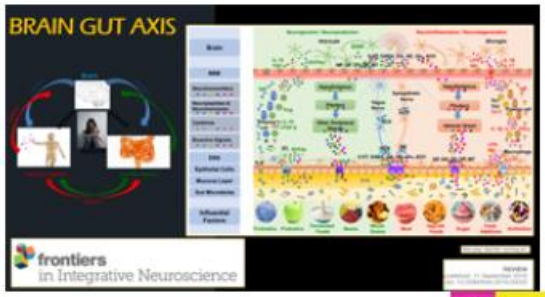
Índice



Complejidad: mentes incorporadas

The BRAIN IMMUNE GUT UNIT (BIGU)

Precision psychiatry: "Not all pacients with X disease are the same"



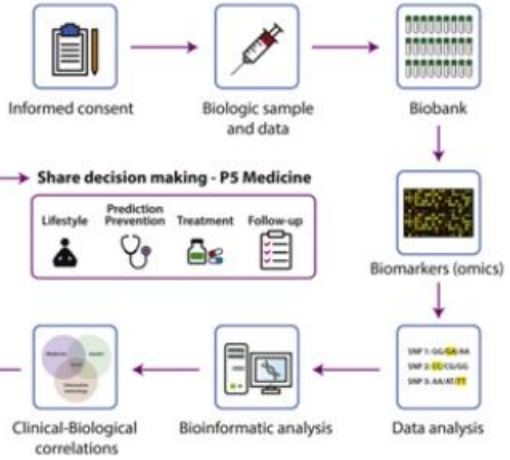


Fig. 1. Steps on the road to personalized medicine.

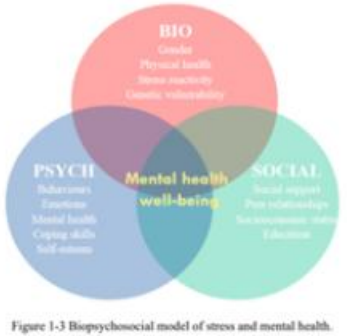
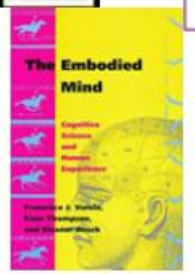


Figure 1-3 Biopsychosocial model of stress and mental health.

Complexity



El mecanismo del estrés

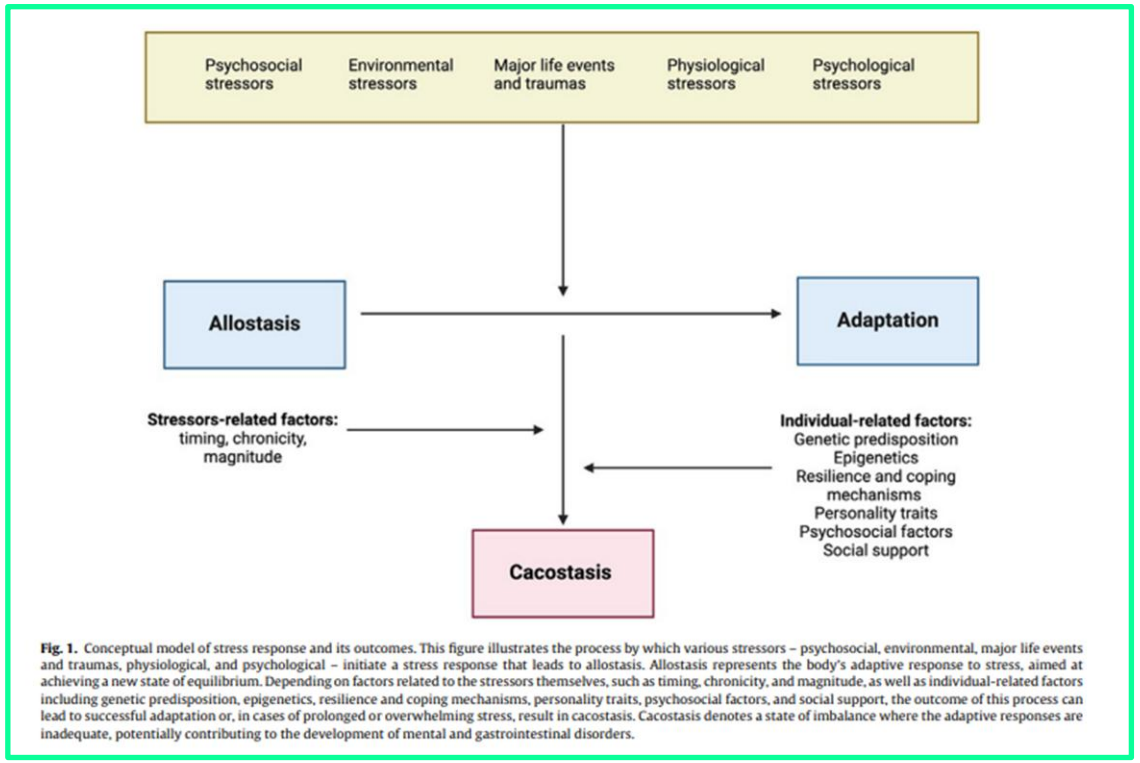


Fig. 1. Conceptual model of stress response and its outcomes. This figure illustrates the process by which various stressors – psychosocial, environmental, major life events and traumas, physiological, and psychological – initiate a stress response that leads to allostasis. Allostasis represents the body's adaptive response to stress, aimed at achieving a new state of equilibrium. Depending on factors related to the stressors themselves, such as timing, chronicity, and magnitude, as well as individual-related factors including genetic predisposition, epigenetics, resilience and coping mechanisms, personality traits, psychosocial factors, and social support, the outcome of this process can lead to successful adaptation or, in cases of prolonged or overwhelming stress, result in cacostasis. Cacostasis denotes a state of imbalance where the adaptive responses are inadequate, potentially contributing to the development of mental and gastrointestinal disorders.

Santos J et al. ttps://doi.org/10.1016/j.medcli.2024.11.023

El mecanismo del estrés-HPA

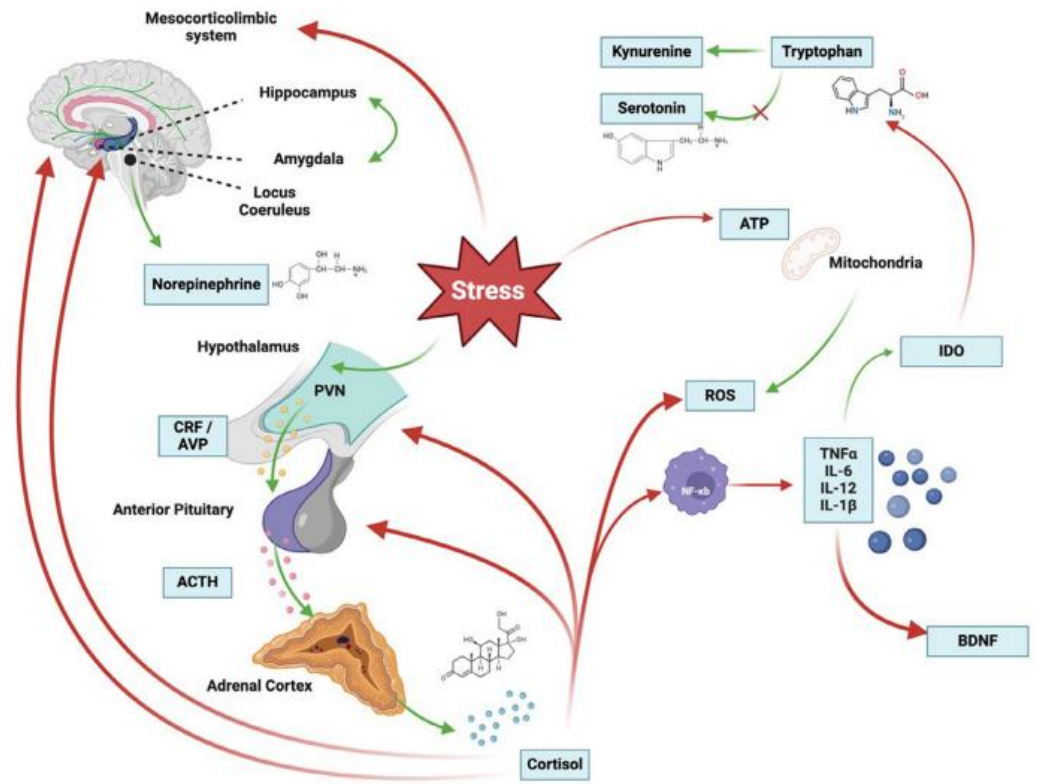


Fig. 2. Stress response and its effects on brain and peripheral systems. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis to release corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) from the paraventricular nucleus (PVN) of the hypothalamus. CRF stimulates the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn triggers cortisol release from the adrenal cortex. Cortisol autoregulates its own release by acting on the pituitary, hypothalamus, and hippocampus to down-regulate the secretion of CRH and ACTH, respectively. Cortisol also modulates the mesocorticolimbic system, hippocampus, amygdala, and locus coeruleus, leading to norepinephrine release. Stress also impacts mitochondrial function, reducing ATP production and increasing the generation of reactive oxygen species (ROS). These ROS activate nuclear factor kappa B (NF-κB), which enhances the production of pro-inflammatory cytokines such as TNFα, IL-6, IL-12, and IL-1β, thereby influencing the immune response. Additionally, stress alters the metabolism of tryptophan, shunting it away from serotonin production towards the kynurenine pathway via indoleamine 2,3-dioxygenase (IDO), contributing to decreased serotonin levels and potential mood disturbances. Brain-derived neurotrophic factor (BDNF), a crucial factor for neuroplasticity, is also modulated by stress, linking the stress response to potential neuropsychiatric outcomes.

Santos J et al. ttps://doi.org/10.1016/j.medcli.2024.11.023

El mecanismo del estrés-HPA

HOW DOES CHRONIC STRESS HARM THE GUT? NEW CLUES EMERGE

A bacterium in the intestines of stressed mice interferes with cells that protect against pathogens.

By Max Kozlov

Mental stress has long been linked to flare-ups of gastrointestinal conditions such as irritable bowel syndrome (IBS). Now, researchers have uncovered exact details of one way that stress can harm the intestines – by setting off a biochemical cascade that reshapes the gut microbiome (W. Wei *et al. Cell Metab.* https://doi.org/md4v; 2024).

Their study, published on 22 January, is nice, says Christoph Thaiss, a microbiologist and neuroscientist at the University of Pennsylvania in Philadelphia. It highlights how the brain – despite being far away from the gastrointestinal tract – can still influence it.

IBS, which causes abdominal pain and diarrhoea, affects one in ten people. Up to ten million people worldwide have inflammatory bowel disease, which causes inflammation of the intestines and triggers similar symptoms. Study co-author Xiao Zheng, a metabolism researcher at the China Pharmaceutical University in Nanjing, wanted to understand what happens on the cellular level to trigger these conditions.

He and his colleagues exposed mice to chronic stress for two weeks and observed the effects. The animals ended up with reduced

The small intestine's lining has finger-like structures that help to absorb nutrients.

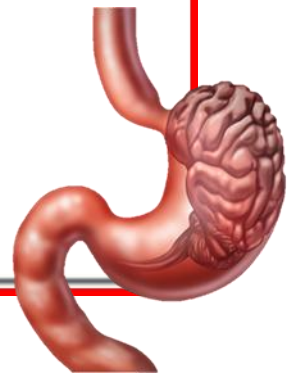
make the chemical indole-3-acetate (IAA). The researchers found that a raised level of IAA, triggered by stress, prevented the mouse intestinal stem cells from becoming protector cells.

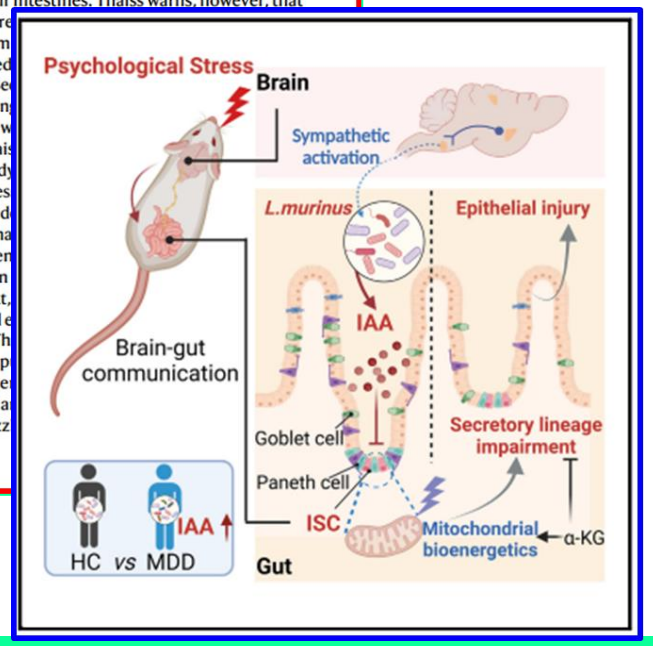
A piece of the puzzle

Although this study was conducted in mice, the researchers gathered evidence that their findings might hold true for humans: the team found elevated levels of both *Lactobacillus* bacteria and IAA in the faeces of people with depression, compared with samples from people without it. "When we suffer from stress, our gut microbiome is also suffering from stress," Zheng says.

The authors also found a possible antidote, in mice at least. When they gave stressed mice a supplement called α-ketoglutarate, which is taken by some bodybuilders, it kick-started the metabolism of the impaired stem cells in their intestines. Thaiss warns, however, that

> "When we suffer from stress, our gut microbiome is also suffering from stress."





Highlights

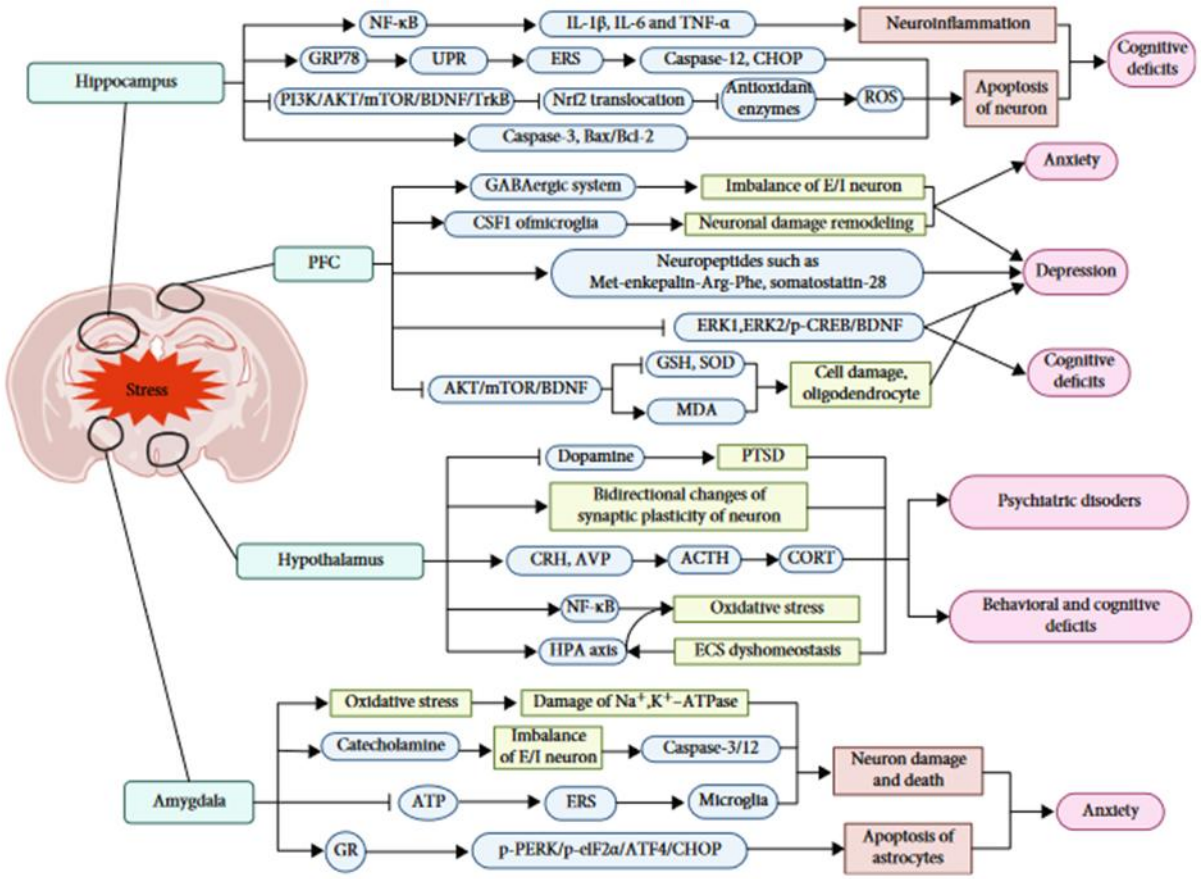
- Psychological stress shapes ISC fate decision via gut microbial remodeling
- Microbial IAA acts on ISC mitochondria to impede secretory cell lineage commitment
- Supplementation of α-ketoglutarate rescues both IAA and stress-induced ISC defect
- IAA production is increased in the gut of patients with mental stress

El mecanismo del estrés-daño cerebral y factor riesgo para enfermedad mental

Table 2: Neurological links between stress and key brain regions.

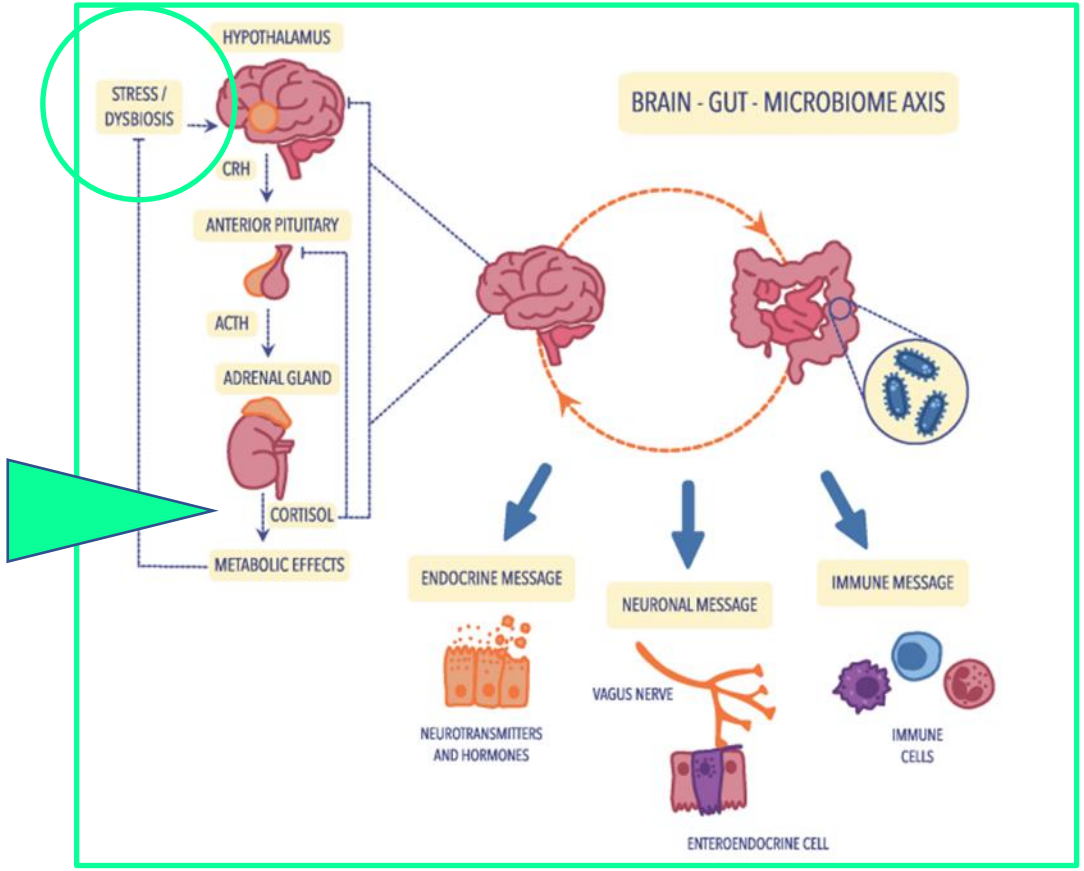
Brain region	Stress model	Neurological dysfunction and mechanism	Reference
Hippocampus	CUMS, CRS	Spatial memory deficits, cognitive impairments, and affective disorder ERS-mediated apoptosis of hippocampal neurons↑, caspase-3↑, Bax/Bcl-2↑ Protein/lipid peroxidation↑ and SOD↓ PI3K/AKT/mTOR-mediated BDNF/TrkB↓ NF-κB↑, IL-1β↑, IL-6↑, and TNF-α↑ CA3 apical dendritic atrophy	[3, 37–40, 47, 57–59]
Hypothalamus	Acute stress, PPS, RS	Cognitive and behavioral deficits Overactivation of HPA axis nNOS mRNA↑ and SOD↓ Bidirectional changes in synaptic plasticity of PVN neuroendocrine cells Dopamine↓, dyshomeostasis of ECS Behavioral and cognitive deficits, even psychiatric disorders	[43, 60–67, 171]
Amygdala	CRS, social isolation stress, RS	Social anxiety, cognitive dysfunctions, and neurodegenerative disorders Imbalance of E/I neurons Activation of ERS of neurons and astrocytes Astrocyte apoptosis↑ Persistent oxidative status ATP↓, GR, CHOP, caspase-12↑ Overactivation of microglia ERS-mediated GABAergic BBB damage	[4, 76–80]
PFC	CUMS, ELS	Emotional disorders such as depression and anxiety E/I imbalance of neurons, neuropeptides↓ ERK-CREB-BDNF signal pathway↓ MDA↑, GSH↓, SOD↓, and BDNF↓	[55, 83–86, 90, 91]

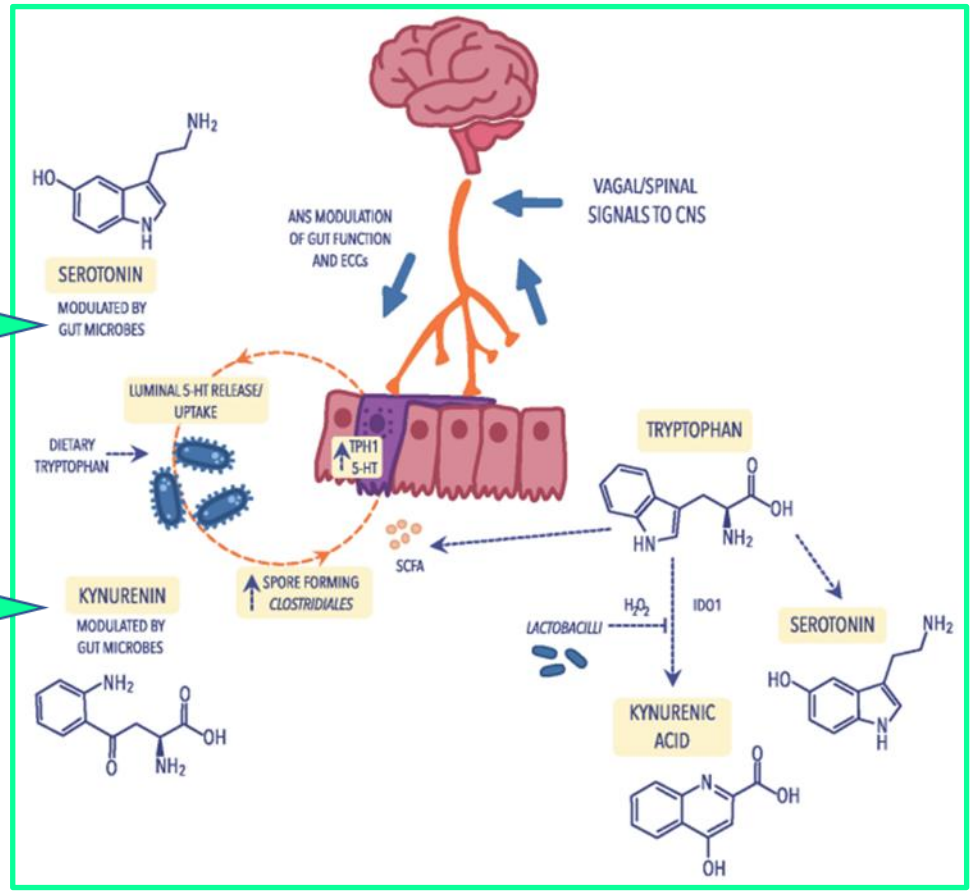
Note: PFC: prefrontal cortex; CRS: chronic restraint stress; RS: restraint stress; PPS: predator-based psychosocial stress; CUMS: chronic unpredictable mild stress; MS: maternal separation; ELS: early life stress; GABA: γ-aminobutyric acid; BBB: blood-brain barrier: ERS: endoplasmic reticulum stress; ECS: endocannabinoid system; HPA: hypothalamus-pituitary-adrenal axis; E/I: excitatory/inhibitory; ↑: upregulated; ↓: downregulated.



Hindawi
Oxidative Medicine and Cellular Longevity
Volume 2022, Article ID 8111022, 17 pages
https://doi.org/10.1155/2022/8111022

El eje cerebro-inmune-intestino-microbiota





Int. J. Mol. Sci. **2022**, 23, 11245. https://doi.org/10.3390/ijms231911245

El eje cerebro-inmune-intestino-microbiota: el link inflamación-microbioma

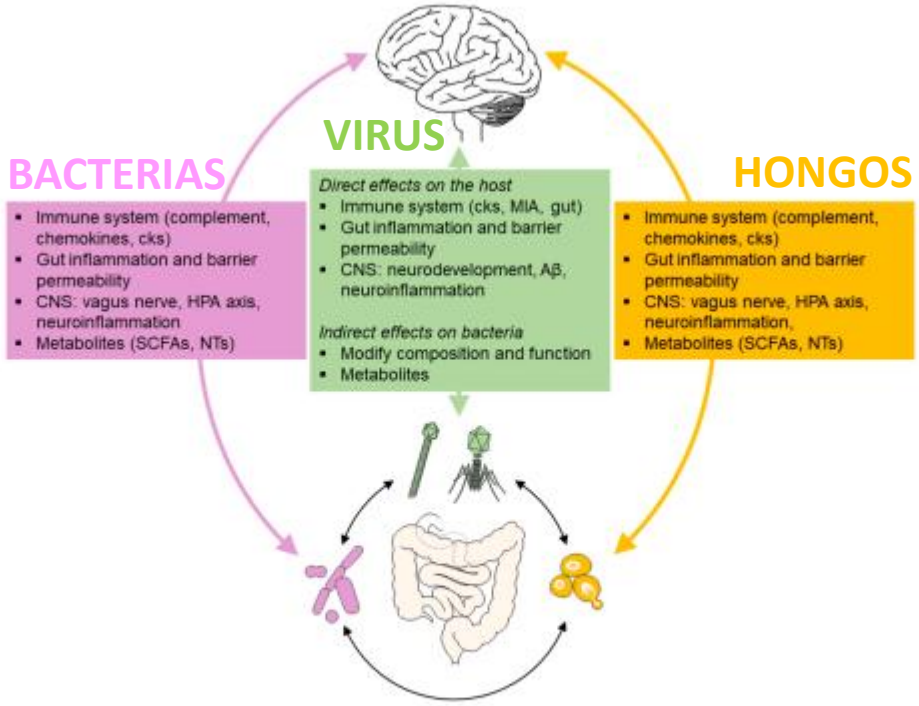


Fig. 2. Mechanisms of the microbiota-gut-brain (MGB) axis, summarising the bidirectional effects between the members of the metagenome (bacterial, viral, and fungal) and the CNS (Motifolio Illustration Toolkits). Cks – cytokines, CNS – central nervous system, HPA – hypothalamic–pituitary–adrenal, SCFAs – short-chain fatty acids, NTs – neurotransmitters, MIA – maternal immune activation, Aβ – amyloid beta. Pink – bacteria, green – viruses (including phages), yellow – fungi. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Malan-Müller et al.

Brain, Behavior, and Immunity 123 (2025) 510–523

El eje cerebro-inmune-intestino-microbiota y enfermedad mental

- ✓ Estudios en animales muestran que la microbiota intestinal influye en el desarrollo y la maduración del cerebro y los estados mentales (Diaz Heijtz et al., 2011; Borre et al., 2014; Galland, 2014; Mu et al., 2016; Manderino et al., 2017; Bruce-Keller et al., 2018).
- ✓ El estrés altera la composición de la microbiota y, al revés, que el microbioma intestinal también regula la respuesta al estrés en una especie de loop bidireccional.
- ✓ Los animales libres de gérmenes (GF) presentan defectos de desarrollo en la estructura cerebral y un desarrollo mental anormal (Diaz Heijtz et al., 2011; Desbonnet et al., 2014; Ogbonnaya et al., 2015; Hoban et al., 2016; Luczynski et al., 2016; Chen et al., 2017).
- ✓ Parto vaginal vs parto por cesárea
- ✓ Uso de Antibióticos
- ✓ La microbiota está relacionada con numerosos trastornos mentales como los trastornos de la conducta alimentaria, los trastornos depresivos o la esquizofrenia.

BIGA & depresión

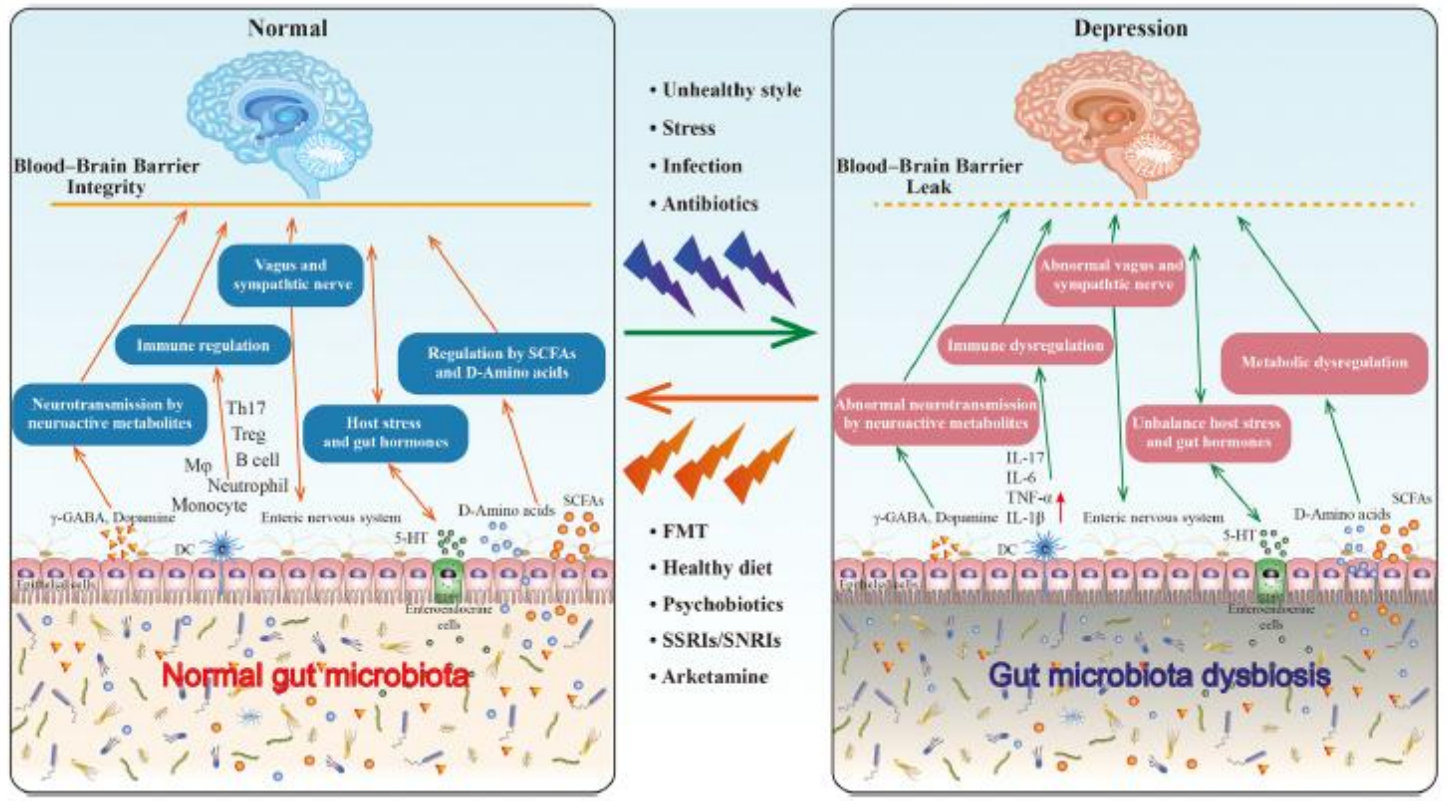


Fig. 2. The role of the brain–gut–microbiota axis in depression. An unhealthy lifestyle due to increased and sustained stress, infection, or other factors can cause dysbiosis of the gut microbiota. Abnormal conditions in the body may be bidirectionally regulated by the brain–gut–microbiota axis via neural signals, immune signals, or chemical signal, thereby contributing to depression. Research has demonstrated that fecal microbiota transplantation (FMT), diet, psychobiotics, and antidepressants (e.g., SSRIs, SNRIs, arketamine) can restore abnormalities in the gut microbiota, abnormal brain function, and depressive symptoms via the brain–gut–microbiota axis. CNS: central nervous system, DC: dendritic cell, 5-HT: 5-hydroxytryptamine, IL-6: interleukin 6, IL-17: interleukin 17, IL-1β: interleukin 1β, SCFA: short chain fatty acid, TNF-α: tumor necrosis factor α. With slight modifications from the articles (Cenit et al., 2017; Wei et al., 2021).

1-Modulación de Neurotransmisores
2-Modulación Inmunológica
3-Regular HPA
4-Regular productos/metabolitos (SCFA, N Vago, Neuroendocrinos)

MDD & Sistema inmunológico: Fenotipado

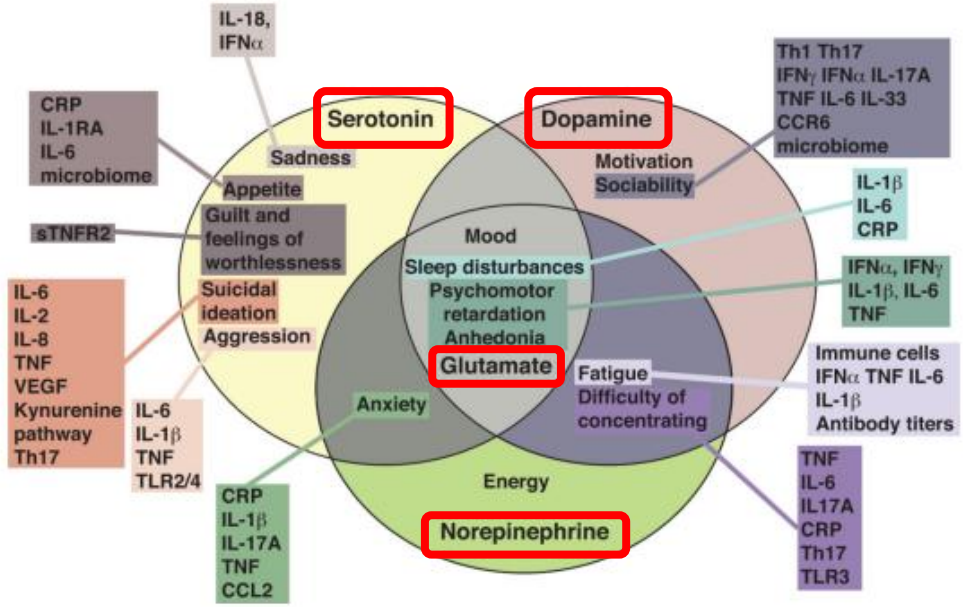


Figure 1. Symptoms of Depression Associated with Different Immunological Changes
Monoamine neurotransmitters have been associated with various symptoms of depression as depicted in each oval. Some symptoms are dependent on multiple neurotransmitters, such as psychomotor retardation that is regulated by serotonin, dopamine, norepinephrine, and glutamate. Each box represents the different immunological changes (e.g., cytokines, immune cell, and others) associated with each symptom.

Neuron. 2020 July 22; 107(2): 234–256. doi:10.1016/j.neuron.2020.06.002.

Link SI-Microbioma

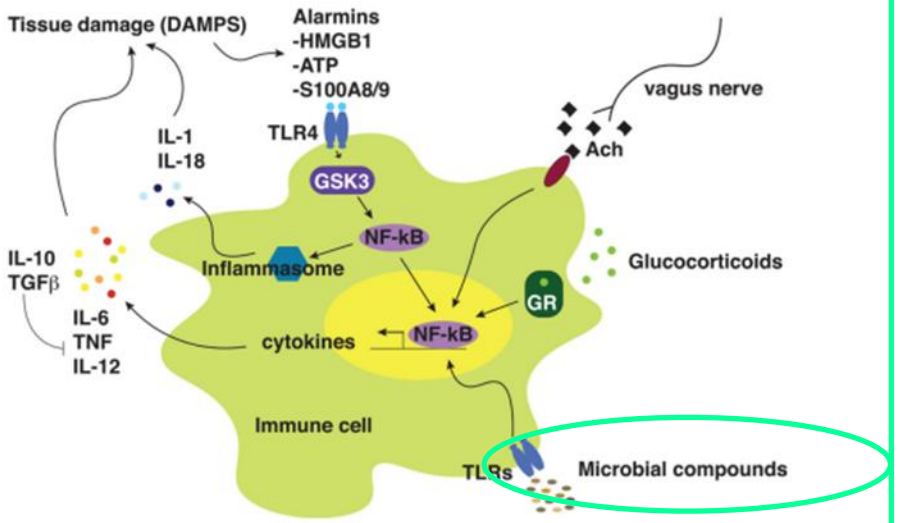


Figure 4. Multiple Mechanisms May Contribute to the Dysregulation of Cytokines in MDD
Immune cell production of cytokines is regulated by multiple mechanisms, including anti-inflammatory actions by glucocorticoids, and vagus nerve pathways, and proinflammatory actions influenced by the microbial composition and stress-induced DAMPs involving both the inflammasome and the NF-κB pathways. Ach, acetylcholine; ATP, adenosine triphosphate; DAMP, danger-associated molecular pattern; GR, glucocorticoid receptor; GSK3, glycogen synthase kinase-3; HMGB1, high-mobility group binding protein-1; IL, interleukin; NF-κB, nuclear factor-kappa B; TLR, Toll-like receptor; TGF, transforming growth factor; TNF, tumor necrosis factor

Neuron. 2020 July 22; 107(2): 234–256. doi:10.1016/j.neuron.2020.06.002.

Microbioma y depresión

Molecular Psychiatry (2016), 1–11

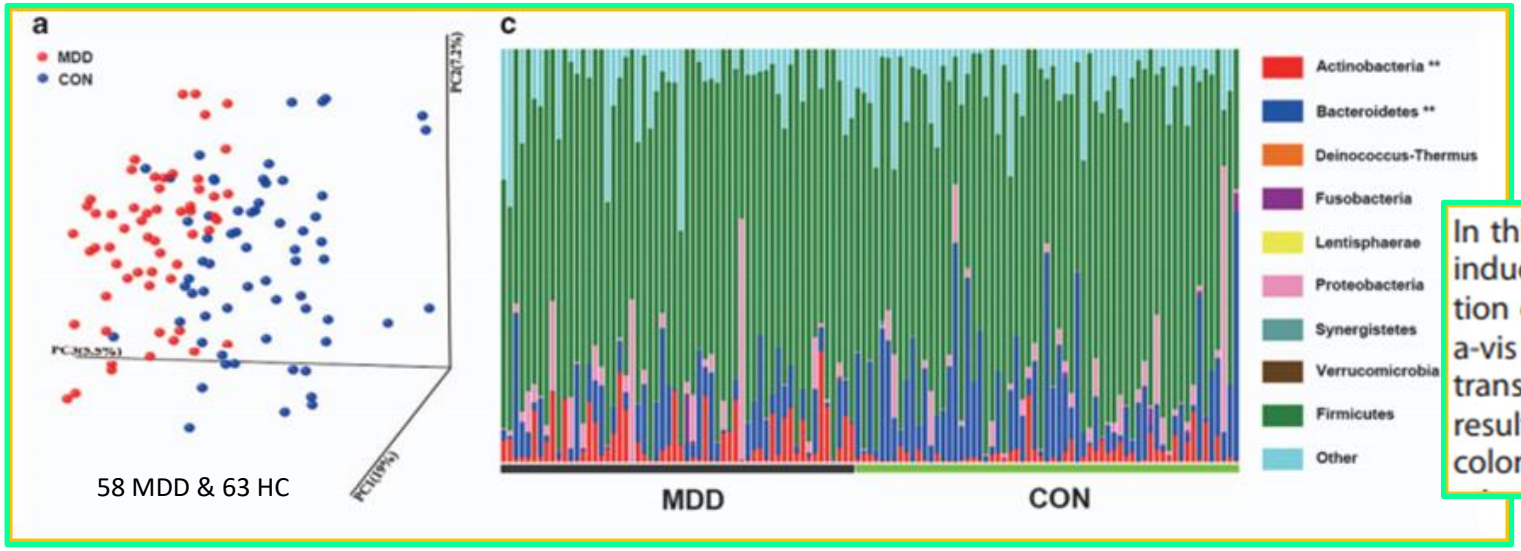
www.nature.com/mp

ORIGINAL ARTICLE

Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism

P Zheng[1,2,3,8], B Zeng[4,8], C Zhou[1,2,3,8], M Liu[1,2,3], Z Fang[1,2,3], X Xu[1,2,3], L Zeng[1,2,3], J Chen[1,2,3], S Fan[1,2,3], X Du[1,2,3], X Zhang[1,2,3], D Yang[5], Y Yang[1,2,3], H Meng[6], W Li[4], ND Melgiri[1,2,3], J Licinio[7,9], H Wei[4,9] and P Xie[1,2,3,9]

- ✓ GFM conductas depresivas
- ✓ Personas con MDD microbioma alterado
- ✓ Transmision de fenotipo depresivo a ratones



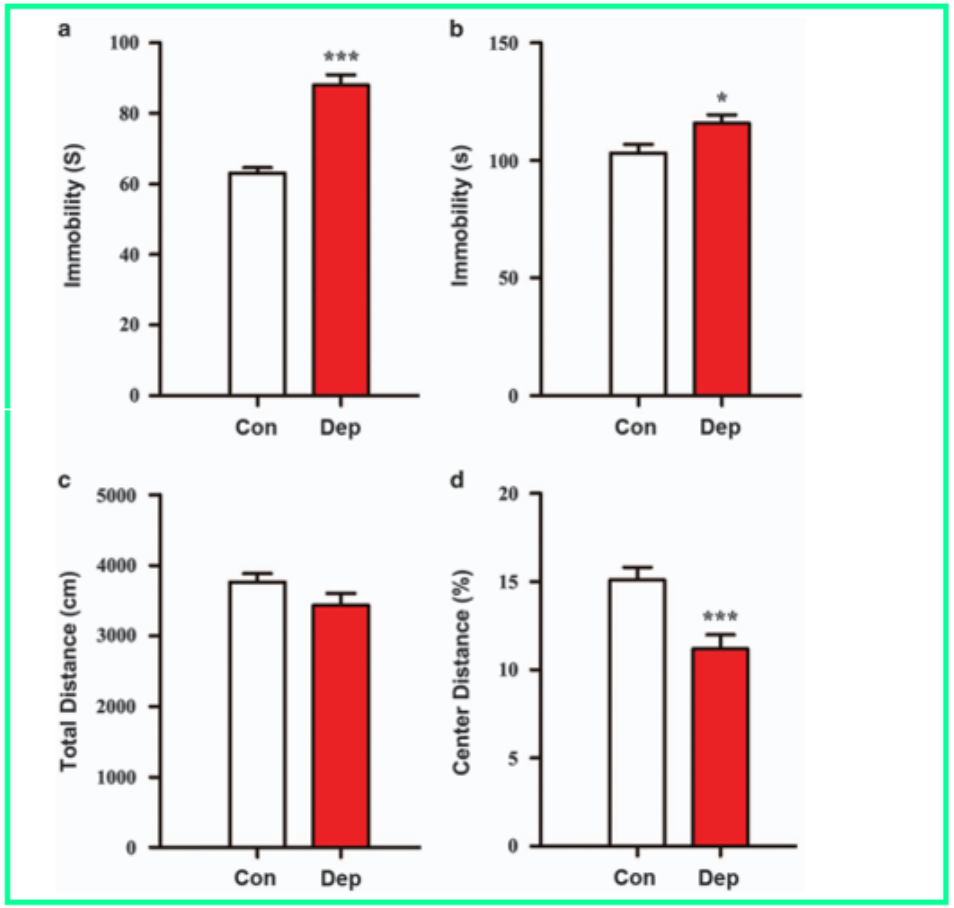
58 MDD & 63 HC

In this study, we demonstrate that the absence of gut microbiota induces depression-like behavior in mice and that the composition of gut microbiota is significantly altered in MDD patients vis-a-vis healthy control individuals. More notably, this alteration was transmissible: colonization of GF mice with 'depression microbiota' resulted in increased depression-like behaviors as compared with colonization with 'healthy microbiota'. Mice harboring 'depression

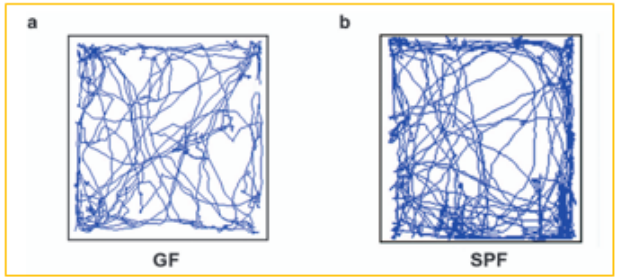
Microbioma y depresión

Force swim test

- Male patients=5
- Male controls=5
- 1week/2 Week after FMT



Overall locomotor activity



Open field test

Zheng et al. Moelcular Psychiatry. 2016

Asociacion, no causalidad.

Systematic Review of Gut Microbiota and Major Depression

Stephanie G. Cheung[1,2], Ariel R. Goldenthal[2,3], Anne-Catrin Uhlemann[4,5], J. John Mann[2,3,6], Jeffrey M. Miller[2,3] and M. Elizabeth Sublette[2,3]*

[1] Division of Consultation-Liaison Psychiatry, Columbia U... Columbia University, New York, NY, United States, [3] Mol... Institute, New York, NY, United States, [4] Division of Infec... New York, NY, United States, [5] Microbiome & Pathogen... [6] Department of Radiology, Columbia University, New Y...

Altered Composition of Gut Microbiota in Depression: A Systematic Review

Zahra Amirkhanzadeh Barandouzi[1,2]*, Angela R. Starkweather[1,2], Wendy A. Henderson[1,2], Adwoa Gyamfi[1] and Xiaomei S. Cong[1,2]

[1] School of Nursing, University of Connecticut, Storrs, CT, United States, [2] Center for Advancement in Managing Pain, School of Nursing, University of Connecticut, Storrs, CT, United States

Alpha and beta diversity findings were inconsistent.

The neuroactive potential of the human gut microbiota in quality of life and depression

Mireia Valles-Colomer[1,2], Gwen Falony[1,2], Youssef Darzi[1,2], Ettje F. Tigchelaar[3], Jun Wang[1,2], Raul Y. Tito[1,2,4], Carmen Schiweck[5], Alexander Kurilshikov[3], Marie Joossens[1,2], Cisca Wijmenga[3,6], Stephan Claes[5,7], Lukas Van Oudenhove[7,8], Alexandra Zhernakova[3], Sara Vieira-Silva[1,2,9] and Jeroen Raes[1,2,9]*

- ✓ Butyrate-producing Faecalibacterium and Coprococcus bacteria were consistently associated with higher quality of life indicators.
- ✓ Dialister & Coprococcus spp. Lower in depression.

Research

JAMA Psychiatry | Original Investigation

Perturbations in Gut Microbiota Composition in Psychiatric Disorders
A Review and Meta-analysis

Viktoriya L. Nikolova, MRes; Megan R. B. Smith, BSc; Lindsay J. Hall, PhD; Anthony J. Cleare, MBBS, PhD; James M. Stone, MBBS, PhD; Allan H. Young, MD, PhD

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis found that gut microbiota perturbations were associated with a transdiagnostic pattern with a depletion of certain anti-inflammatory butyrate-producing bacteria and an enrichment of pro-inflammatory bacteria in patients with depression, bipolar disorder, schizophrenia, and anxiety.

Pro-inflamación

Anti-inflamación

nature microbiology ARTICLES
https://doi.org/10.1038/s41564-018-0337-x

JAMA Psychiatry. 2021;78(12):1343-1354. doi:10.1001/jamapsychiatry.2021.2573
Published online September 15, 2021. Last corrected on December 5, 2022.

Microbioma-inflamación en MDD

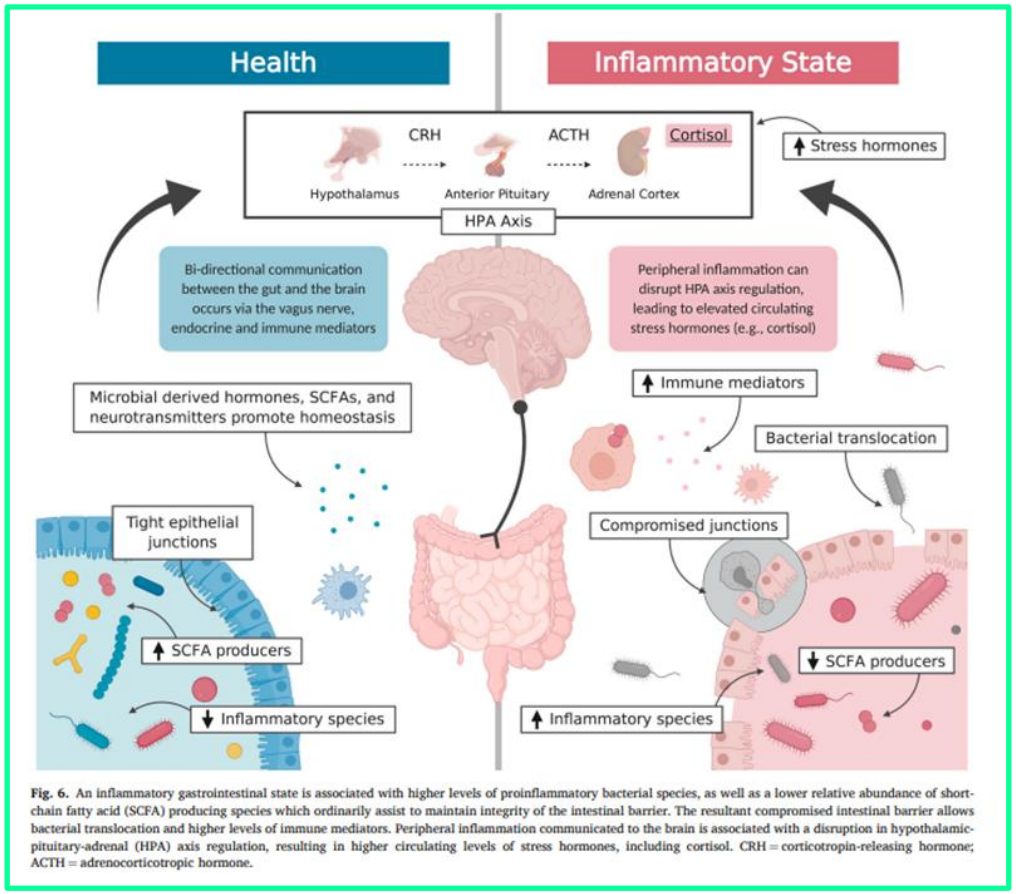
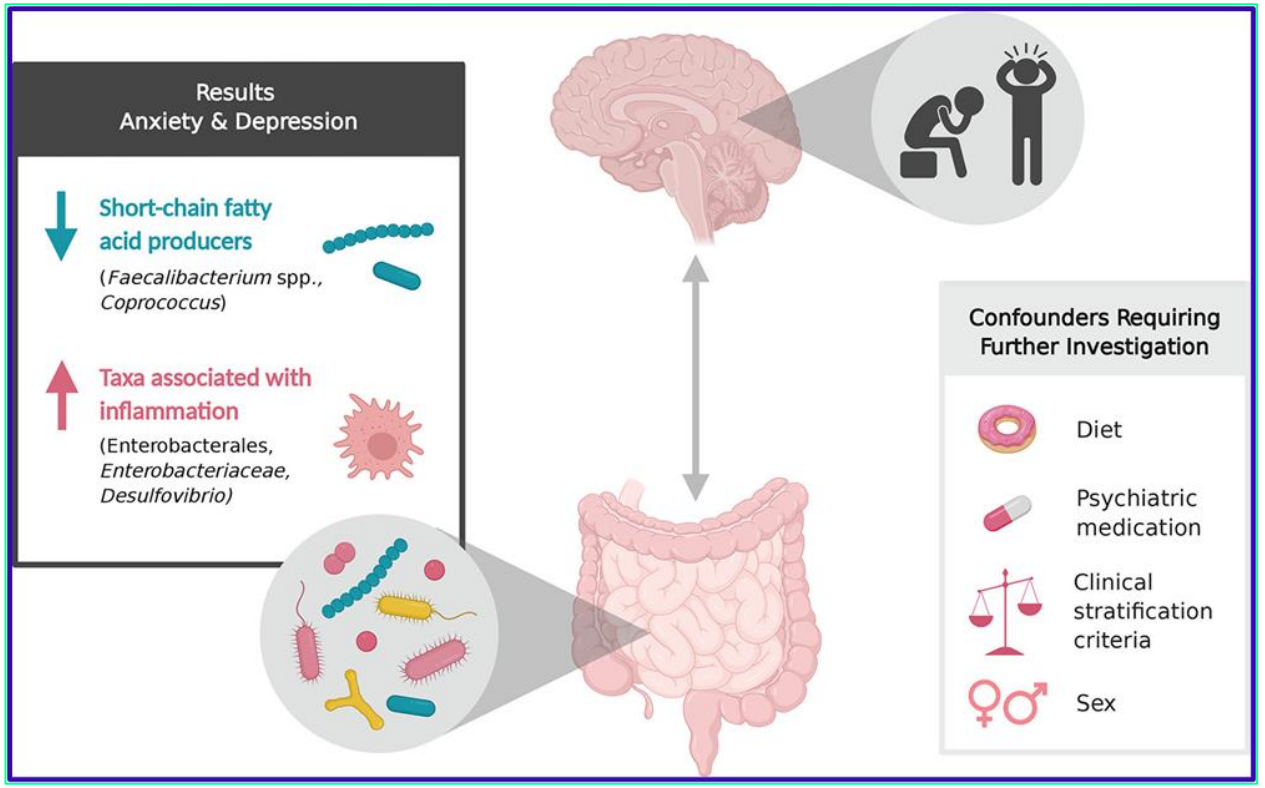


Fig. 6. An inflammatory gastrointestinal state is associated with higher levels of proinflammatory bacterial species, as well as a lower relative abundance of short-chain fatty acid (SCFA) producing species which ordinarily assist to maintain integrity of the intestinal barrier. The resultant compromised intestinal barrier allows bacterial translocation and higher levels of immune mediators. Peripheral inflammation communicated to the brain is associated with a disruption in hypothalamic-pituitary-adrenal (HPA) axis regulation, resulting in higher circulating levels of stress hormones, including cortisol. CRH = corticotropin-releasing hormone; ACTH = adrenocorticotropic hormone.



https://doi.org/10.1016/j.cpr.2020.101943

Potenciales terapéuticos del BIGA en depresión

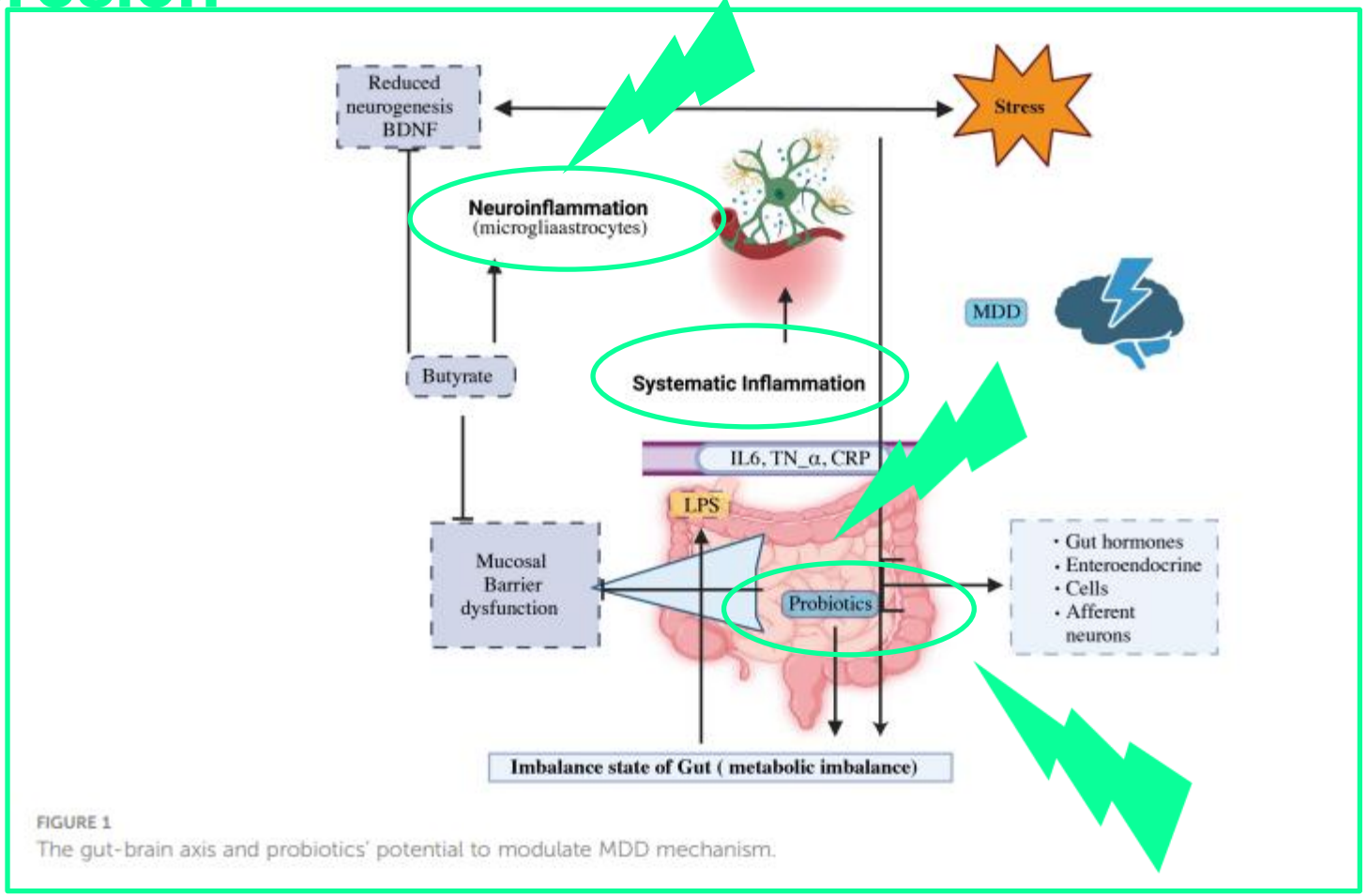


FIGURE 1
The gut-brain axis and probiotics' potential to modulate MDD mechanism.

¿Taquifilaxis?

ScienHub
frontiers | Frontiers in Psychiatry
TYPE Review
PUBLISHED 09 February 2024
DOI 10.3389/fpsyt.2024.1295766

Microbioma-inflamación en MDD

Novel and emerging treatments for major depression

Steven Marwaha, Edward Palmer, Trisha Suppes, Emily Cons, Allan H Young, Rachel Upthegrove

Depression is common, costly, debilitating, and associated with increased risk of suicide. It is one of the leading global public health problems. Although existing available pharmacological treatments can be effective, their onset of action can take up to 6 weeks, side-effects are common, and recovery can require treatment with multiple different agents. Although psychosocial interventions might also be recommended, more effective treatments than those currently available are needed for people with moderate or severe depression. In the past 10 years, treatment trials have developed and tested many new targeted interventions. In this Review, we assess novel and emerging biological treatments for major depressive disorder, evaluate their putative brain and body mechanisms, and highlight how close each might be to clinical use.

Lancet 2023; 401: 141–53

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(Prof S Marwaha PhD, E Palmer MBBS, E Cons MSc,

THE LANCET

	Class	Summary of current evidence	Effect size or OR (CI)	Category of evidence
Intravenous ketamine	NMDA modulators	A systematic review and meta-analysis of seven RCTs and 12 open-label trials showed a positive effect of ketamine on MDD[33]	Pooled OR at 7 days 6·33 (95% CI 3·33 to 12·05)	1
Intranasal esketamine	NMDA modulators	A systematic review[79] of five RCTs contained three RCTs that assessed outcome at 28 days of treatment (one showed a significant positive effect), one relapse-prevention study that showed a positive effect, and one open-label, long-term trial that showed a positive effect of esketamine on TRD	For the 28-day outcome studies, significant LSMD of MADRS score −4·0 (95% CI −7·31 to −0·64), p=0·02,[34] and non-significant LSMDs of MADRS score −3·2 (95% CI −6·88 to 0·45), p=0·002[80] and −3·6 (95% CI −7·20 to 0·07), p=0·059;[28] for the relapse-prevention study, risk of relapse HR 0·49 (95% CI 0·29 to 0·84), p=0·003[28]	1
Dextromethorphan and bupropion	NMDA modulators	One phase 2 trial[34] and one phase 3 trial[35] showed positive effects of augmentation in treatment-resistant depression	Phase 2 trial LSMD of MADRS score at 6 weeks of treatment −5·2 (95% CI −9·3 to −1·1); phase 3 trial at 6 weeks of treatment LSMD of MADRS score −3·87 (95% CI −6·36 to −1·39), p=0·002	2
Esmethadone	NMDA modulators	One phase 2a trial showed a positive effect of augmentation in MDD[36]	LSMD of MADRS score at 14 days −10·4 (90% CI −16·1 to −4·6), p=0·0039	2
rTMS (multiple modalities)	Brain stimulation	Nine meta-analyses of 58 primary studies showed a positive effect in treatment-resistant depression[40]	rTMS modalities were more effective than sham treatment for all outcomes; absolute relative risk reduction 23% (95% CI 15% to 32%), NNT 4	1
tDCS	Brain stimulation	A meta-analysis of eight RCTs showed a positive effect of tDCS on MDD[35]	OR 1·96 (95% CI 1·30 to 2·95)	1
Deep brain stimulation	Brain stimulation	A meta-analysis of 14 studies—all small and many not randomised—showed a positive effect of deep brain stimulation regardless of location of stimulation; one RCT of deep brain stimulation targeting the ventral capsule and ventral striatum showed no significant difference in response rates in TRD[81]	For the RCT, change in MADRS score in the active treatment group was 8·0 points (SD 13·7; 19·6% to 34·9% improvement) and change in MADRS score in the sham treatment group was 9·1 points (SD 10·6; 24·6% to 28·8% improvement)	2
Brexanolone	GABA modulators	Three RCTs[41,42] showed a positive effect in post-partum depression	For one RCT, mean difference after 60 h of treatment (HAM-D) −12·2 (95% CI −20·77 to −3·67), p=0·0075, effect size 1·2; for another RCT, LSMD (HAM-D) after 60 h of treatment −5·5 (95% CI −8·8 to −2·2), p=0·0013; for the third RCT LSMD (HAM-D) after 60 h of treatment −2·5 (95% CI −4·5 to −0·5), p=0·0160	2
Glucosamine	GABA modulators	A single, open-label, pilot study showed no significant effect of glucosamine on MDD[43]	Significant change in MADRS score after 2 and 4 week of treatment F=15·80, df=2·18, p<0·001; HAM-D F=14·42, df=2·18, p<0·001; magnitude of improvement was small and there was no significant change in global improvement scores	3
Omega-3 unsaturated fatty acid	Anti-inflammatory agents	A meta-analysis of 12 RCTs showed a positive effect of omega-3 unsaturated fatty acid on MDD[45]	SMD −0·35 (95% CI −0·60 to −0·09), p=0·008; there was moderate study heterogeneity	1
Minocycline	Anti-inflammatory agents	A meta-analysis of three RCTs showed a positive effect of minocycline on MDD[45]	SMD −0·79 (95% CI −1·29 to −0·28), p=0·002; there was moderate study heterogeneity	1
Statins (eg, lorvastatin, atorvastatin, and simvastatin)	Anti-inflammatory agents	A meta-analysis of three RCTs showed a positive effect of statins on MDD when administered with an SSRI;[45] a different meta-analysis of ten studies of statins compared with placebo had high heterogeneity and eight studies with high risk of bias, but showed a positive effect of statins on depressive symptoms in MDD[51]	SMD −0·65 (95% CI −0·96 to −0·33), p<0·0001; there was low study heterogeneity; SMD −0·796 (95% CI −1·107, −0·486), p=0·0001	1
Celecoxib	Anti-inflammatory agents	A meta-analysis of four RCTs[45] showed a positive effect of celecoxib on MDD when administered with an SSRI; with small pooled relative risk, publication bias and mixed quality were highlighted; an RCT showed no benefit of celecoxib over a placebo[47]	For the meta-analysis, SMD −0·76 (95% CI −1·14 to −0·39), p<0·0001; there was low study heterogeneity; for the RCT, mean adjusted difference (HAM-D) at 12 weeks follow-up 1·48 (95% CI −0·41 to 3·36), p=0·123	1
Aspirin	Anti-inflammatory agents	A large RCT of depression prevention in individuals older than 65 years in the USA and Australia showed a small negative effect of aspirin on the risk of developing MDD[48]	HR during 5 years follow-up 1·02 (95% CI 0·96 to 1·08), p=0·54	1
Ayahuasca	Psychedelics	One small RCT[75] and one open-label study showed a positive effect of ayahuasca on TRD	For the RCT, on day 7 of follow-up after a single dose d=0·98 (95% CI 0·21 to 1·75), p=0·019	2
Psilocybin	Psychedelics	One RCT and one open-label study in a meta-analysis[79] showed a positive effect of psilocybin on TRD; one RCT comparing psilocybin with escitalopram showed no superiority;[46] one phase 2 RCT showed a positive effect of psilocybin on MDD[82]	For the meta-analysis, Hedges' g=2·190 (1·42 to 2·96), p<0·001; for the RCT, between-group difference after 6 weeks of follow-up 2·0 (−5·0 to 0·9), p=0·17; for the phase 2 RCT, remission rates after 12 weeks of follow-up were 29% in the 25 mg of psilocybin group compared with 7% in the 1 mg of psilocybin group	2

GABA=γ-amino butyric acid. HR=hazard ratio. HAM-D=Hamilton Depression Rating Scale. LSMD=least square mean difference. MADRS=Montgomery-Åsberg Depression Rating Scale. MDD=major depressive disorder. NMDA=N-methyl-D-aspartate. NNT=number needed to treat. OR=odds ratio. RCT=randomised controlled trial. rTMS=repetitive transcranial magnetic stimulation. SMD=standardised mean difference. SSRI=selective serotonin reuptake inhibitor. tDCS=transcranial direct current stimulation. TRD=treatment-resistant depression. There are four categories of evidence for causal relationships and treatment.[82]

Potenciales terapéuticos del BIGA en depresión

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Exploring the gut-brain Axis: Potential therapeutic impact of Psychobiotics on mental health

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1. Regula HPA
2. Inmunomodulan/Reducen inflamación
3. Induce una mayor producción de diversos compuestos farmacológicamente activos como neurotransmisores, proteínas, SCFAs…

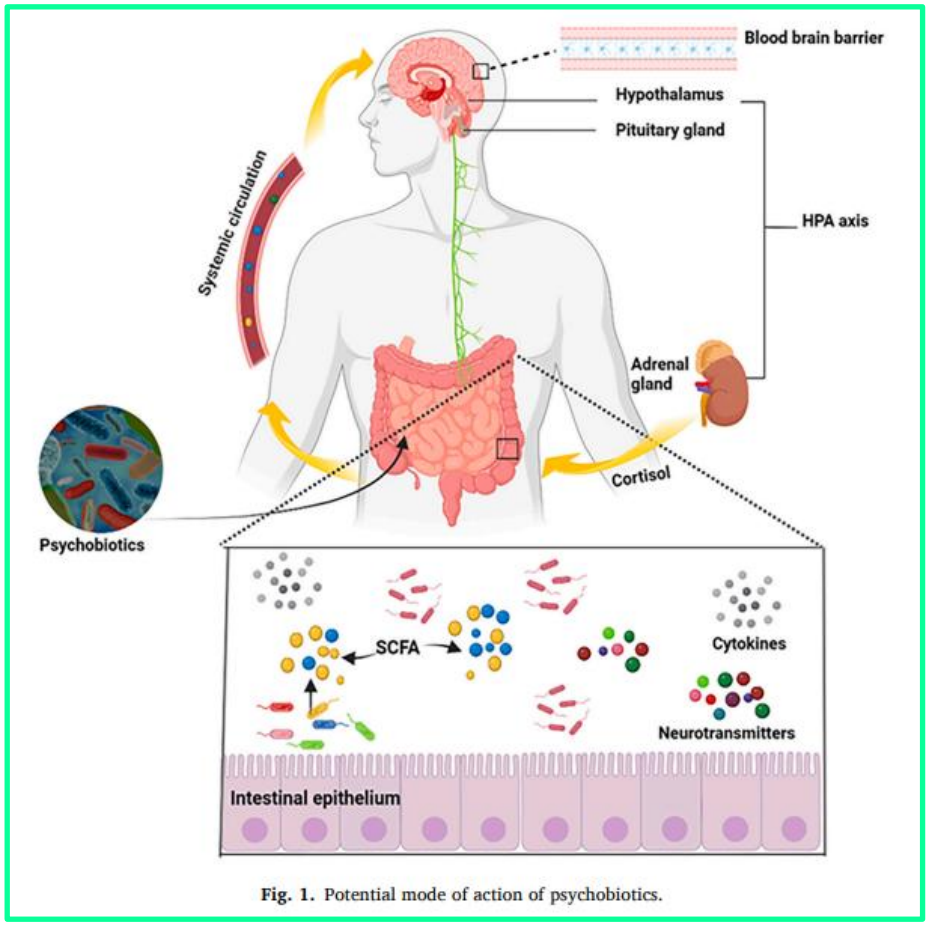

Fig. 1. Potential mode of action of psychobiotics.

REVIEW

Molecular Nutrition & Food Research
www.mnf-journal.com

Psychobiotics for Mitigation of Neuro-Degenerative Diseases: Recent Advancements

Priya Dhyani, Chhaya Goyal, Sanju Bala Dhull, Anil Kumar Chauhan, Baljeet Singh Saharan, Harshita, Joginder Singh Duhan, and Gulden Goksen**

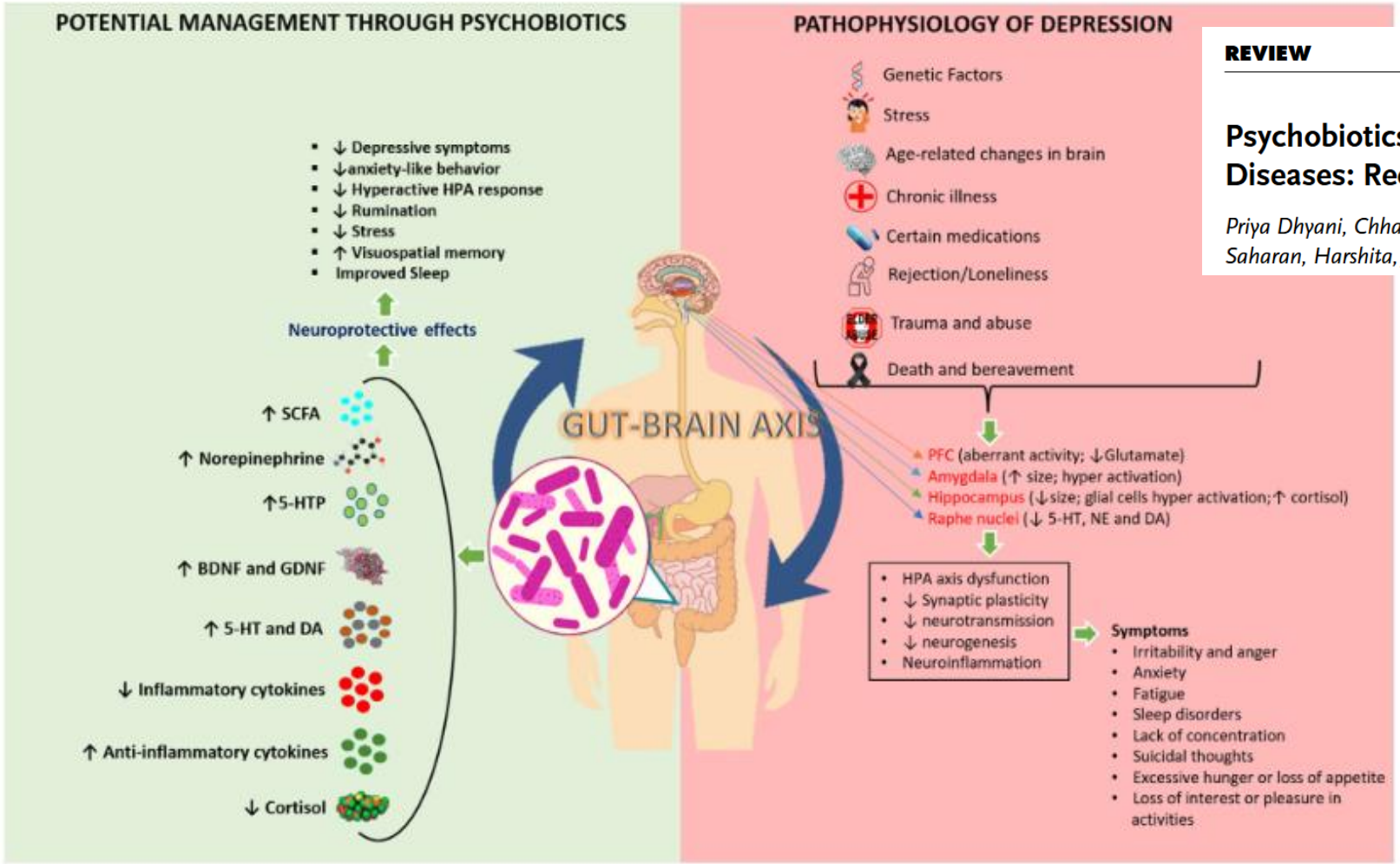

Figure 3. Pathophysiology of depression in elderly people and possible mechanism of action of psychobiotics in its management. Various factors (genetics, stress, chronic illness, trauma, abuse, rejection, etc.) may lead to a decrease in the production of 5-HT, NE, and DA in Raphe nuclei, a decrease in the size of the hippocampus, enlargement of the amygdala, and aberrant neural activity in the PFC. This in turn leads to HPA axis dysfunction, neuroinflammation, and reduced synaptic plasticity, which result in the typical symptoms of depression. Psychobiotic intervention provides neuroprotective effects via the production and/or stimulation of the production of anti-inflammatory cytokines, SCFA, NE, 5-HT, 5-HTP, cortisol, BDNF, and GDNF and decreasing the production and/or activity of inflammatory cytokines. This in turn reduces stress, anxiety, and other depressive symptoms. 5-HT-serotonin, 5-HTP-5-hydroxytryptophan; BDNF, brain-derived neurotrophic factor; DA, dopamine; GDNF, glial cell-line derived neurotrophic factor; HPA, hypothalamic-pituitary-adrenal; NE, norepinephrine; PFC, prefrontal cortex; SCFA, short chain fatty acid.

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ORIGINAL INVESTIGATION

OPEN ACCESS

Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals: The World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce

Jerome Sarris[a,b,c], Arun Ravindran[d], Lakshmi N. Yatham[e], Wolfgang Marx[f], Julia J. Rucklidge[g], Roger S. McIntyre[h], Shahin Akhondzadeh[i], Francesco Benedetti[j,k], Constanza Caneo[l], Holger Cramer[m], Lachlan Cribb[b], Michael de Manincor[a], Olivia Dean[f,n], Andrea Camaz Deslandes[o], Marlene P. Freeman[p], Bangalore Gangadhar[q], Brian H. Harvey[r], Siegfried Kasper[s], James Lake[a,t], Adrian Lopresti[u], Lin Lu[v], Najwa-Joelle Metri[a], David Mischoulon[w], Chee H. Ng[b], Daisuke Nishi[x,1], Roja Rahimi[y], Soraya Seedat[z], Justin Sinclair[a], Kuan-Pin Su[aa,ab], Zhang-Jin Zhang[ac,ad] and Michael Berk[c,f,ae]

Guias Clinicas

these agents. Finally, the taskforce noted that such use of nutraceuticals or phytoceuticals be primarily recommended (where supportive evidence exists) adjunctively within a standard medical/health professional care model, especially in cases of more severe mental illness. Some meta-analyses reviewed contained data from heterogenous studies involving poor methodology. Isolated RCTs and other data such as open label or case series were not included, and it is recognised that an absence of data does not imply lack of efficacy.

Results: Amongst nutraceuticals with Grade A evidence, positive directionality and varying levels of support (*recommended, provisionally recommended,* or *weakly recommended)* was found for adjunctive omega-3 fatty acids (+++), vitamin D (+), adjunctive probiotics (++), adjunctive zinc (++), methylfolate (+), and adjunctive s-adenosyl methionine (SAMe) (+) in the treatment of unipolar depression. Monotherapy omega-3 (+/−), folic acid (−), vitamin C (−), tryptophan

microorganisms

MDPI

Review

Probiotics' Effects in the Treatment of Anxiety and Depression: A Comprehensive Review of 2014–2023 Clinical Trials

Ermis Merkouris [1], Theodora Mavroudi [1], Daniil Miliotas [1], Dimitrios Tsiptsios [1,2], Aspasia Serdari [3], Foteini Christidi [1], Triantafyllos K. Doskas [4], Christoph Mueller [5,6] and Konstantinos Tsamakis [5,7,*]

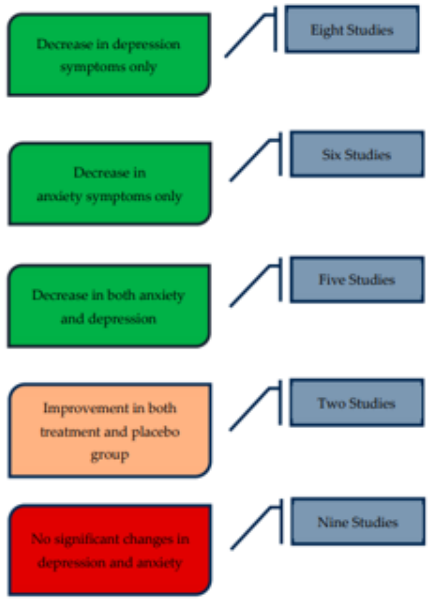
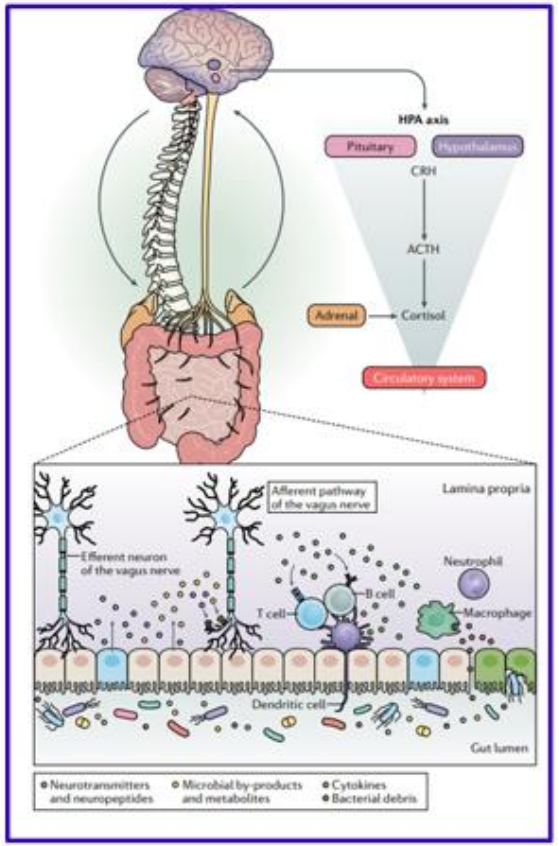


Figure 2. Clinical outcomes of probiotic use in anxiety and depression.

- ✓ 2/3 estudios dan soporte con evidencia moderada.
- ✓ Mas beneficio en leves/moderados.
- ✓ Mecanismo antiinflamatorio implicado.
- ✓ ¿Cual de ellos usar, dosis, cepas?
- ✓ Tratamiento único vs complementario.
- ✓ No hay un unico microorganismo implicado
- ✓ Elaborar consenso de expertos/guías clínicas

The gut microbiota–brain axis in behaviour and brain disorders

Livia H. Morais, Henry L. Schreiber IV and Sarkis K. Mazmanian



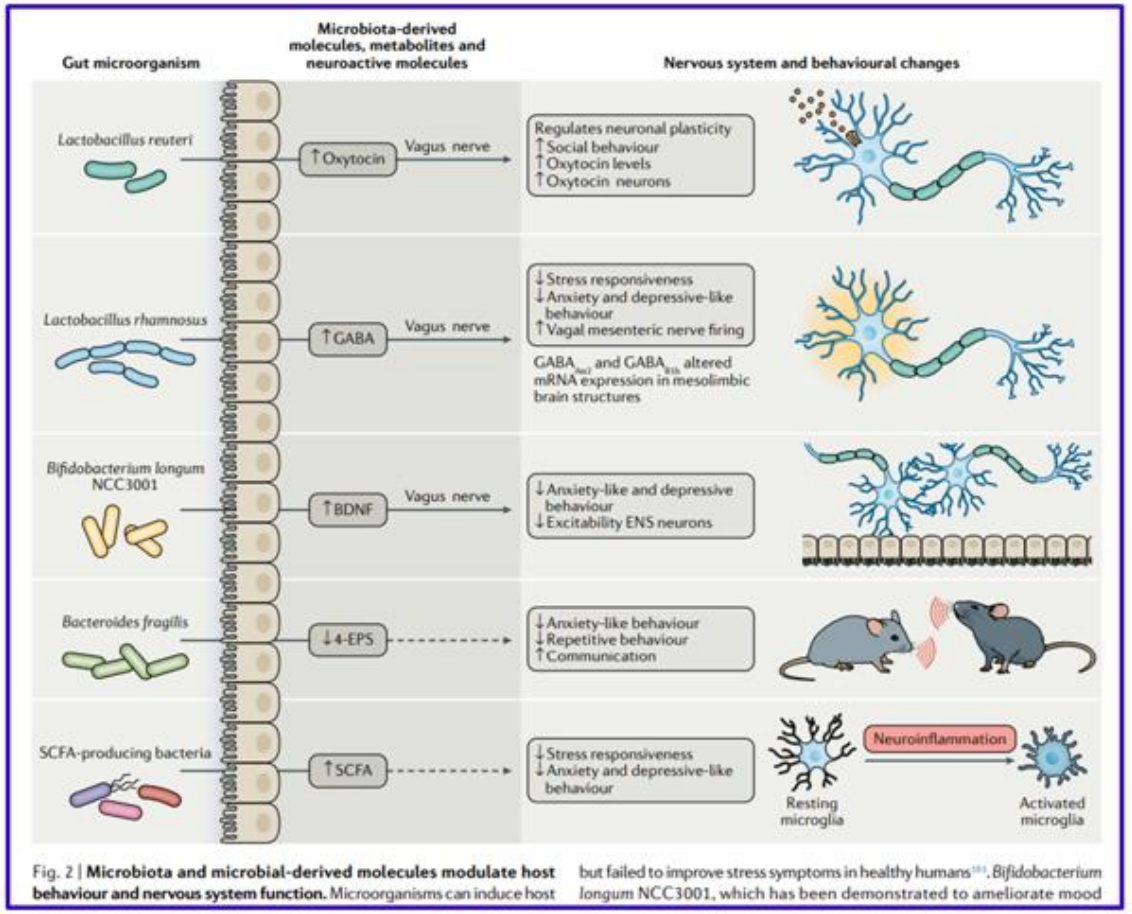
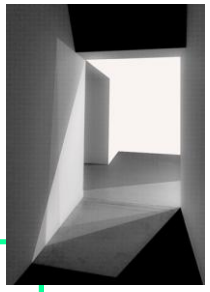


Fig. 2 | **Microbiota and microbial-derived molecules modulate host behaviour and nervous system function.** Microorganisms can induce host but failed to improve stress symptoms in healthy humans[161]. *Bifidobacterium longum* NCC3001, which has been demonstrated to ameliorate mood

- ✓ B.longum, breve, infantis
- ✓ L. casei, paracasei, helveticus, plantarum, rhamnosus…



Pan et al. BMC Psychiatry (2025) 25:64
https://doi.org/10.1186/s12888-024-06438-z

BMC Psychiatry

SYSTEMATIC REVIEW Open Access

Efficacy and safety of gut microbiome-targeted treatment in patients with depression: a systematic review and meta-analysis

Bo Pan[2,3†], Yiming Pan[2,3†], Yu-Song Huang[4†], Meng Yi[2], Yuwei Hu[2,3], Xiaoyu Lian[2,3], Hui-Zhong Shi[6], Mingwei Wang[2,3], Guifen Xiang[2,3,5], Wen-Yi Yang[4*], Zhong Liu[2,3,5*] and Fangfang Xia[1*]

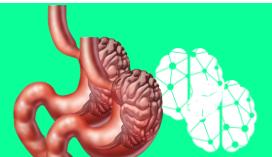
- ✓ MTT **significantly improve** depressive symptoms
- ✓ Significantly **modulated** biochemical indicators, including BDNF, CRP, cortisol, and IL-6
- ✓ However, there was a **high heterogeneity** in the present study

- ✓ underpowered studies, methodological heterogeneity, varying depression diagnostic criteria
- ✓ Lack of consideration of confounding variables
- ✓ Inappropriate statistical analysis, and functional redundancy of the microbiota.
- ✓ A limitation of the vast majority of previous studies includes the use of 16S-RNA-seq, which does not have enough taxonomic resolution to report results at the species level and does not provide information about microbial functionality.

Conclusions

Even though MTT was overall effective in the treatment of depression with acceptable safety, we remained cautious in drawing this conclusion, limited by the small sample of included studies and heterogeneity. Efficacy of MTT for depression varies by geography, patient comorbidities, and administration duration. Future trials with larger sample sizes are needed to confirm the true clinical potential of MTT for depression.

Cell Metabolism 37, 138–153, January 7, 2025



Chinna Meyyappan *et al. BMC Psychiatry* (2020) 20:299
https://doi.org/10.1186/s12888-020-02654-5

BMC Psychiatry

RESEARCH ARTICLE Open Access

Effect of fecal microbiota transplant on symptoms of psychiatric disorders: a systematic review

Arthi Chinna Meyyappan[1,2,3*], Evan Forth[1,2,3], Caroline J. K. Wallace[1,2,3] and Roumen Milev[1,2,3,4]

There is a great need for new therapeutic targets and treatments in order to provide options and better help individuals suffering from these psychiatric illnesses. When considering the findings demonstrated in this review, FMT appears to be a promising candidate for this. The ongoing research certainly suggests its efficacy and given the few side effects and adverse events reported in these papers, may even challenge the treatments currently available. Though the treatment effect seems

Conclusion

With high individual variability in symptomatology and prognosis, high levels of comorbidity with other disorders, genetic *and* environmental influences, progress in research in treatment of psychiatric disorders has been challenging. Given the huge heterogeneity of psychiatric disorders, finding treatment that works for all patients is not achievable, especially given the range of factors that influence the disorder and treatment response. While the research in this field is far from complete, the potential of targeting the gut-brain axis using FMT to alleviate symptoms of psychiatric illness is promising. Additionally, given the adaptable nature of the gut microbiome, it may be a good representation of the individual's history and could explain differences in risk of illness, disease course, and response to treatment. If these therapies are able to alleviate symptoms of psychiatric disorders, they could be offered to some patients as personalized, alternative, and/or adjunctive treatments to combat specific symptoms that tie together specific gut bacteria strains or the gut, as a whole, to the brain.

Retos

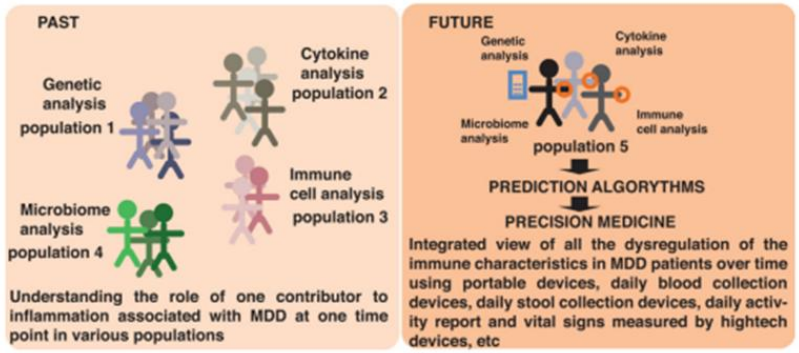


Figure 5. Where the Field Is Going

Historically many studies of immunological factors that may affect MDD focused on a single component, such as genetic variables, cytokines, immune cell types or actions, and the microbiome composition. With technological advances that have recently become available, or are under development, we envision that researchers will be able to apply a more integrated approach to analyze multiple parameters in each individual subject to obtain a more complete and integrated picture of genetic, microbial, and immunological factors that influence the onset, course, and treatment response of MDD patients.

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EXPERT REVIEW

Check for updates

The gut microbiome and mental health: advances in research and emerging priorities

Andrew P. Shoubridge[1,2], Jocelyn M. Choo[1,2], Alyce M. Martin[3], Damien J. Keating[3], Ma-Li Wong[4], Julio Licinio[4,5] and Geraint B. Rogers[1,2]✉

- ✓ Complejidad
- ✓ Prevalencia in crescendo
- ✓ Tratamientos insuficientes-Taquifilaxis
- ✓ Patologías resistentes
- ✓ Urgen nuevas dianas terapéuticas farmacológicas y no farmacológicas
- ✓ Rol BGA prometedor

Neuron. 2020 July 22; 107(2): 234–256. doi:10.1016/j.neuron.2020.06.002.

The BRAIN IMMUNE GUT UNIT (BIGU)

¡Muchas gracias por la atención!

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