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The Microbiota-Inflammasome Hypothesis of Major Depression

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Abstract

We propose the “microbiota-inflammasome” hypothesis of major depressive disorder (MDD, a mental illness affecting the way a person feels and thinks, characterized by long-lasting feelings of sadness). We hypothesize that pathological shifts in gut microbiota composition (dysbiosis) caused by stress and gut conditions result in the upregulation of pro-inflammatory pathways

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mediated by the Nod-like receptors family pyrin domain containing 3 (NLRP3) inflammasome (an intracellular platform involved in the activation of inflammatory processes). This upregulation exacerbates depressive symptomatology and further compounds gut dysbiosis. In this review we describe MDD/chronic stress-induced changes in: 1) NLRP3 inflammasome; 2) gut microbiota; and 3) metabolic pathways; and how inflammasome signaling may affect depressive-like behavior and gut microbiota composition. The implication is that novel therapeutic strategies could emerge for MDD and co-morbid conditions. A number of testable predictions surface from this microbiota-gut-inflammasome-brain hypothesis of MDD, using approaches that modulate gut microbiota composition via inflammasome modulation, fecal microbiota transplantation, psychobiotics supplementation, or dietary change.

Keywords

depression; dysbiosis; gut microbiota; inflammasome; NLRP3; probiotics

1. Introduction

The NLRP3 inflammasome is an intracellular immune sensor capable of detecting stress, danger, or damage.[1] NLRP3 inflammasomes are present in many immune cell types (including microglial cells, monocytes, granulocytes, epithelial cells, and T and B cells), and once activated, they trigger intracellular cascades that return the system to homeostasis.[2] One of the main avenues through which NLRP3 exerts its effect is via the activation of interleukin-1 beta (IL1B)-mediated cascades.[3] As IL1B signaling is a crucial node in the gut-immune-brain communication, understanding NLRP3 function, and dysfunction has become essential to understanding health and disease across a range of contexts, including MDD.[2,3] Converging evidence supports a role for the NLRP3 inflammasome in stress responses and the development of depressive symptomatology and systemic illnesses.[1,4,5]

We hypothesize a mechanism by which stress exposure, via influencing the gut microbiome, affects NLRP3- and IL1B- driven pathways to modulate brain function. These processes lead to depressive- and anxiety-like behavior that increase the risk of MDD and associated co-morbidities (Figure 1). We further hypothesize that, through NLRP3-mediated pathways, stress results in alteration of gut microbiota composition, further compounding pathogenic processes that lead to MDD. A framework for investigating this hypothesis is set out in this article.

2. The Microbiota-Gut-Inflammasome-Brain Axis

The microbiome-gut-brain axis consists of a communication network that controls and integrates gut and brain function, and that seems to be a central modulator of health and disease.[6] More specifically, there seems to exist a bidirectional communication between the gut and the brain, which occurs through multiple intertwined pathways, mediated by the vagus nerve,[7] the immune system,[8,9] and the bacterial metabolome (the ensemble of bacterial metabolic by-products and end products).[10,11]

Recently, the role of the gut microbiome in shaping behavior, its interconnectedness with brain processes, and its potential involvement in the pathophysiology of MDD have come to the forefront in psychiatry.[12–14] The term microbiome refers to all bacteria, bacterial genomes, and bacterial metabolites and byproducts present in a specific habitat at any given point.[15] Its phylogenetic composition is determined by both selective pressure form the host and microbial competition.[16]

The microbiota-gut-inflammasome-brain (MGIB) axis is a bidirectional communication system, that links psychological stress responses, immune system function, and gut microbiome composition.[9] Exposure to stress increases NLRP3 signaling, which activates IL1- and TNF-mediated pathways.[17,18] These increase pro-inflammatory signaling in stress-responsive brain areas and activate the hypothalamic-pituitary-adrenal (HPA) axis, exacerbating anxiety, and depressive behaviors.[17,19–21] However, the extent to which NLRP3 signaling is activated appears to be greatly influenced by the composition and function of the gut microbiome, an entity independently linked to MDD risk and co-morbidities.[9,10,12,22–25]

3. MDD is Associated with Altered Gut Microbiota Composition

Increasing evidence suggests that MDD is associated with altered gut microbiology, and the majority of the studies that have investigated the “depression microbiota” have reported compositional differences between depressed patients and healthy controls. Typically, alterations in overall microbiota structure, rather than in the abundance of individual species, have been described (for a summary of studies reporting bacterial changes in MDD patients, see Table 1).

A recent study reported similar dysbiotic signatures between irritable bowel syndrome (IBS), MDD, and IBS/MDD co-morbid patients.[26] Patients were assigned to three subgroups depending on their microbiota profile. Two of these subgroups (totaling 80% of MDD patients and 85% of IBS patients) were characterized by lower bacterial diversity, expanded representation of *Bacteroides* or *Prevotella* bacterial genera, and increased colonic inflammation. The third group showed relatively balanced microbiota composition and no overt immune activation.[26]

In a Chinese cohort, Jiang and colleagues[27] reported greater bacterial diversity in active MDD patients, when comparing active depressed patients, depressed patients responding to treatment and healthy controls. Proteobacteria were increased in active MDD patients, while Firmicutes were reduced. *Proteus mirabilis* (a Proteobacteria phylum member) is known to trigger NLRP3 activation and IL1B production.[24] Bacterial components from other Proteobacteria, such as the lipopolysaccharide (LPS) produced by *Pseudomonas* species, trigger depressive symptoms via NLRP3 inflammasome activation and production of LPS-reactive immunoglobulins. Notably, levels of these pro-inflammatory markers are increased in MDD.[25,28]

Bacteroidetes were higher in the active depression group (mostly the result of increased *Parabacteroides* and *Alistipes* abundance). As these bacteria convert tryptophan to indole,

they influence tryptophan availability and might be involved in the serotonergic imbalances observed in MDD.[29] Interestingly, the abundance of the genus *Alistipes* is increased in MDD, chronic fatigue syndrome, IBS and stress models, and appears to correlate with inflammation.[30,31] A diabetogenic effect of this genus has been hypothesized, which could contribute to the MDD-diabetes co-morbidity. Similarly, *Lachnospiraceae*, a key producer of the SCFA butyrate, which helps maintain intestinal barrier integrity, was decreased in this cohort. Such changes might contribute to the increased susceptibility of MDD patients to leaky gut and gastrointestinal pathology.[32,33] The genus *Faecalibacterium*, is a well-recognized suppressor of inflammation, and its lower abundance in MDD patients is consistent with the heightened inflammatory state in MDD.[32,33] *Oscillibacter* was also increased in active MDD patients.[34] This genus produces the short-chain fatty acid (SCFA) valeric acid, which resembles gamma-aminobutyric acid (GABA) and is involved in gastrointestinal functions.[35]

Zheng and colleagues investigated microbiota composition in a Chinese MDD cohort and found alterations of taxa belonging to the phyla Bacteroidetes (decreased in MDD), Actinobacteria (increased in MDD), and Firmicutes (some members increased and others decreased in MDD).[10] The authors performed fecal microbiota transplantation (FMT) from MDD patients to germ-free mice, and mice receiving the “depression microbiota” displayed increased anxiety and depressive-like behavior. These findings suggest that the depressive phenotype is transmissible via the gut microbiome.

Given that sex-based differences exist in MDD, a study in a Chinese cohort investigated sex-driven differences in microbiome composition in MDD.[36] The main findings were an overrepresentation of Actinobacteria in female MDD patients compared to female controls and an underrepresentation of Bacteroidetes in male MDD patients compared to male controls.[36] In keeping with the findings of Zheng and colleagues (above),[10] Firmicutes levels were altered irrespective of sex, suggesting that disrupted Firmicutes equilibria might represent a hallmark of MDD.[10,36] Moreover, the authors found a positive correlation between *Colinsella* abundance and the severity of depressive symptoms.[36] Other authors have reported a decrease of this genus after antidepressant intervention, suggesting that *Colinsella* might represent a useful index for MDD management and treatment.[36,37] Another study in a small cohort from the same group reported partly contrasting findings, given that Firmicutes, Actinobacteria, and Lachnospiraceae were increased in MDD patients, while Bacteroidetes and Proteobacteria were reduced.[38] The authors concluded that such differences might have stemmed form different sample size, demographics, and statistical approach.[38]

Kelly and colleagues investigated the depression microbiota using an Irish MDD cohort. In contrast to the findings of Jiang and colleagues, the authors reported decreased bacterial diversity in the MDD group compared to healthy controls, which were associated with an increase in inflammatory markers.[39] Using a similar approach to Zheng and colleagues, the authors demonstrated that FMT from MDD patients to antibiotic-treated rats recapitulated the depressive phenotype. Rats receiving depression-associated microbiota displayed anhedonic- and anxiety-like behavior, and MDD-like biological traits, including increased plasma kynurenine and plasma kynurenine/tryptophan ratio.[39]

Naseribafrouei and colleagues reported a correlative study of fecal microbiota composition in Norwegian MDD patients and found that the complete microbiota correlated with depression with high predictive accuracy independent of medication status.[34] *Lachnospiracea* and *Bacteroidetes* were under-represented in MDD patients. Low levels of *Bacteroidetes* are associated with chronic low-grade inflammation and obesity, suggesting that such decrease could bridge the chronic low-grade inflammatory status reported in depression and obesity.[40,41]

By demonstrating that altered gut microbiology is associated with depression, these studies provide exciting insight into pathological mechanisms, and opportunities for therapeutical improvements. However, it is important to note the variability in the reported findings. Larger studies that take into consideration factors such as diet and pharmacological treatment are required to corroborate these early investigations, to clearly define MDD-associated microbiome characteristics.

4. MDD is Associated with Altered Metabolic Pathways

The shifts in gut microbiota composition observed in MDD patients result in metabolic pathways disturbances. These include altered amino acid profiles, low- and very low-density lipoproteins, and levels of metabolism-related molecules.[42,43] Interestingly, humanized germ-free mice with MDD microbiota have metabolic signatures that resemble those of the human donors, suggesting that behaviors associated with specific gut microbiota may be transmissible.[10] This intriguing observation raises the question of whether transferring healthy microbiota to depressed individuals could be clinically beneficial. Importantly, microbiota-driven metabolic changes are transmissible and are reflected in the recipient's hippocampus.[10]

5. The Microbiota-Inflammasome Hypothesis of Depression and Co-Morbid Systemic Illnesses

Converging evidence supports a role for the NLRP3 inflammasome in stress responses and the development of depressive symptomatology and systemic illnesses.[1,4,5] This has led to the formulation of the "inflammasome hypothesis of depression."[44] In this hypothesis, psychological stress activates the NLRP3 inflammasome. If protracted, increased systemic inflammation represents a risk for the development of depressive symptomatology and co-morbid illnesses.[44]

However, the inflammasome hypothesis of depression does not take into account the involvement of the gut microbiota in the dysregulation of NLRP3-mediated enteric, central, and systemic inflammatory processes.[9,10,12,24,27,32,34,39,45,46] In fact, evidence exists supporting the bidirectional interactions between the gut microbiota and the immune system, which is mediated at least partially by the NLRP3 inflammasome.[45,47,48]

Here, we put forward the concept that the gut microbiota might play a causal role in the development of MDD. We suggest that stress exposure increases NLRP3 signaling, which in turn increases anxiety and depressive behaviors, and leads to an over-representation of pro-

inflammatory bacterial clades within the gut microbiota composition. Concurrently, stress-induced, inflammation-mediated, changes in the gut microbiome alter the bioavailability of monoamine and neuroactive compounds, further exacerbating depressive symptomatology. By increasing systemic and central NLRP3-mediated pro-inflammatory signaling, gut dysbiosis contributes to both the onset of depressive symptoms and to the risk of NLRP3-related co-morbid disorders (Figure 1 and 2).

The proposed microbiota-inflammasome hypothesis of depression is based on the following notions: a) psychosocial stress increases NLRP3 signaling;[4,23,49,50] b) stress- and/or dysbiosis-mediated changes in gut barrier function result in increased bacterial translocation ("leaky gut") to otherwise sterile enteric compartments, fueling pro-inflammatory signaling;[25,51,52] c) inflammation-mediated shifts in gut microbiota composition alter the availability of microbiota-produced neurotransmitters and neuroactive compounds;[10,12,53] and d) increased NLRP3 activity fueled by chronic stress, dysbiosis, and leaky gut, increases the likelihood of anxiety and depressive behavior, and co-morbid conditions.[44,49,50]

5.1. The Directionality of the Microbiota-Inflammasome Hypothesis of Depression and Co-Morbid Systemic Illnesses

The directionality of this model remains to be elucidated. To the authors, the microbiota-gut-inflammasome-brain axis should be considered as a multidirectional interactive system, in which change implications can be complex and far-reaching.

For example, gut dysbiosis (e.g., irritable bowel disease, IBD) will likely trigger increased pro-inflammatory signaling, which can lead to MDD.[26,54] At the same time, gut dysbiosis will increase the likelihood of developing co-morbid illnesses due to the heightened inflammatory status.[3,55] Conversely, repeated or chronic stress and/or MDD increases pro-inflammatory signaling,[56] which can lead to gut dysbiosis, and increased representation of pro-inflammatory bacterial clades.[4,10,12] The resulting heightened inflammatory state would likely increase the likelihood of developing co-morbid systemic illnesses while fueling depressive symptoms.

6. The NLRP3 Inflammasome is Involved in Psychological Stress Responses and MDD

6.1. The NLRP3 Inflammasome Mediates Psychological Stress Responses

Psychosocial stress triggers sterile inflammation, that is initiated by the release of danger-associated molecular patterns (DAMPs), which "primes" the body and the brain for a potential immune response following damage from confrontation with peers or predators.[57]

DAMPs alert the immune system through pattern recognition receptors (PRRs).[58] This activates inflammasomes, which release IL1B, IL18, and IL33.[2] These cytokines stimulate the hypothalamic-pituitary-adrenal (HPA) axis, which by increasing glucocorticoid release, down-regulates immune responses to return to homeostasis.[59] When exposure to a stressor is repeated or prolonged, NLRP3 activity does not resolve.[23] This can lead to chronic low-grade systemic inflammation, exacerbating depressive symptoms.[60,61] Interestingly,

increased caspase 1 (CASP1) activity is responsible for cleaving glucocorticoid receptors and increasing glucocorticoid resistance, which could contribute to the downregulation of glucocorticoid receptors and resistance to glucocorticoids observed in MDD.[59,62,63] Ultimately, depressive symptoms are compounded by HPA axis dysfunction, functional, and structural brain changes, and gut dysbiosis. These changes fuel systemic inflammation exacerbating anxiety and depressive symptoms and increase the likelihood of co-morbid ill-nesses.[3,12,22,44,47,49–52,55,56,64,65]

6.2. The NLRP3 Inflammasome Regulates Intestinal Homeostasis

The NLRP3 inflammasome plays a key role in intestinal homeostasis and in the mediation of gut-immune-brain communication.[45] NLRP3-produced IL1 and IL18 play fundamental regulatory roles in gut function and dysfunction. In fact, while IL1 and IL18 are involved in maintaining intestinal integrity and epithelium repair, aberrant IL1 and IL18 signaling can become detrimental to gut function.[66–68] Accordingly, mice lacking *Nlrp3* or *Casp1*, display increased mortality to experimental colitis. This is characterized by a loss of epithelial integrity, bacterial dispersion, increased leukocyte infiltration, and upregulated chemokine production.[67,69] These observations suggest that NLRP3 activity is necessary to combat intestinal stress and maintain gut homeostasis.[67,69] Studies have also reported that NLRP3 inflammasome inhibition may have entero-protective effects in experimental colitis.[70] These apparently contrasting findings suggest that the fine-tuning of NLRP3 activity is essential for gut homeostasis, and that NLRP3 modulation (but not total inhibition) might prove valuable in conditions connected to altered inflammatory profiles and dysbiotic states, including MDD.[12]

Genetic evidence further supports the role of NLRP3 inflammasome in chronic inflammatory conditions.[71,72] Given the importance of a fine-tuned NLRP3 activity, this node could represent a new target in modulating gut homeostasis and treating the dysbiotic features that may accompany a subset of MDD cases and co-morbid dysfunctions.[10,12,34]

6.3. The NLRP3 Inflammasome is Involved in the Communication Between Bacterial Metabolites and the Brain

Interactions between commensal microbiota and the host have developed over millennia, and they have a beneficial influence on many aspects of physiology.[73] Disruption of these interactions can precipitate enteric, autoimmune, metabolic, and psychiatric disorders.[9,12,34,74] One of the principal pathways of microbiotagut-brain interaction are the host-microbe metabolic axes, crosstalk networks linking bacterial metabolites and host cellular pathways.[11] Such cross-talk acts principally through: 1) vagus nerve activation by microbiota-produced by-products and metabolites, which directly affect brain function and indirectly regulate immune system balances;[75] and 2) direct interaction of the microbiota and their metabolites with components of the immune system, such as the NLRP3 inflammasome, which influence pathways affecting brain function and behavior.[9,76]

Through such pathways, commensal bacteria can make a substantial contribution to regulating host immunity. For example, many gut commensals, such as spore-forming *Clostridia*, influence intestinal T-regulatory (T-regs) cell through the production of SCFAs.

In turn, T-regs mediate anti-inflammatory and immunoregulatory processes.[77,78] This is particularly relevant for MDD, where shifts toward T-helper 1 (Th1) response have been described in at least a subset of patients.[79,80] Murine studies suggest that some bacterial species (such as *Helicobacter hepaticus*) stimulate pro-inflammatory Th1 and Th17 responses in immunocompromised but not in immunocompetent mice, suggesting that extra attention is needed in shaping therapies in immunocompromised patients.[81]

6.4. The NLRP3 Inflammasome is Involved in MDD

The NLRP3 inflammasome is gaining increasing attention in MDD for its involvement in stress response pathways and gut dysbiosis, which incite depressive symptoms and precipitate comorbid conditions.[23,50,82] A study involving a relatively small cohort of MDD patients and healthy volunteers reported that NLRP3 mRNA and protein is increased in peripheral blood mononuclear cells in MDD patients, together with CASP1 and IL1B levels, and normalized by antidepressant treatment.[60] While this study is yet to be replicated, it corroborates the preclinical evidence that NLRP3 signaling is involved in the development of MDD.[9,23]

6.5. Inflammasome Signaling Modulation Affects Host Behavior and Gut Microbiota Composition

While the potential involvement of the gut-brain axis in the pathophysiology of MDD and in the response to antidepressants is increasingly recognized,[10,27,34,39,83,84] the molecular mechanisms underpinning such communication remain poorly understood. Recently, our group reported that genetic deletion or CASP1 inhibition, and therefore decreased NLRP3 signaling, attenuates anxiety- and depressive-like behaviors, while preventing stress-induced depressive-like behavior in mice.[9] Minocycline treatment resulted in gut microbiota shifts similar to those of *Casp1*$^{-/-}$ mice.[9,46] For example, *Akkermansia,* which attenuates IL1B and IL6 via inducing Foxp3 T-reg cells, was increased in minocycline-treated mice. This is in line with the hypothesis presented here, given that pharmacological inflammasome inhibition resulted in the expansion of bacterial species with immunoregulatory properties.[85] Similarly, Lachnospiraceae, increased in mice receiving stress and minocycline, is considered to be beneficial via the production of anti-inflammatory SCFAs.[85] This supports our hypothesis given that inflammasome inhibition during stress increased a bacterial family that produces anti-inflammatory compounds. Stressed mice showed subtle shifts in the Firmicutes/Bacteroidetes ratio, which correlate to chronic low-grade inflammation.[86] *Bifidobacterium*, a genus associated with inflammatory pathways suppression via nuclear factor NF-kB inhibition, was decreased in stressed mice,[87] while *Lactobacillus*, a genus involved in inflammasome activation via CASP1-mediated IL1B production, was increased.[9] These findings are in line with the proposed hypothesis, and suggest that chronic stress exposure has a deleterious effect on immune processes via increasing the representation of bacterial families that fuel pro-inflammatory and inhibit anti-inflammatory signaling.[9] At the same time, these findings suggest that the pharmacological inhibition of pro-inflammatory pathways during stress exposure could be useful in humans by modulating the effects of stress on gut microbiome composition. Future studies should investigate the therapeutic potential of pharmacological blockade of proinflammatory pathways during

stress to quench the effects of stress-induced inflammation on mental health and gut microbiome composition.

Corroborating the presented hypothesis, a study in cognitively impaired patients found an increased representation of the inflammatory taxon *Escherichia/Shigella* (which positively correlated with NLRP3 and IL1B expression) and a decreased representation of the anti-inflammatory *E. Rectale* (which correlated negatively with IL10) in patients with Alzheimer's disease with brain amyloidosis compared to those without amyloidosis.[88] These findings suggest that the observed shifts in pro- and anti-inflammatory bacterial species and the resulting disruption of cytokine balances might be associated with the heightened inflammatory state observed in patients with brain amyloidosis.

6.6. The NLRP3 Inflammasome Mediates the Cross-Talk Between the Gut Microbiota and the Immune System

While the gut microbiota has a substantial influence on the development and regulation of the immune system, host immunity also helps to shape the composition of the gut microbiota.[48,89] The majority of immune pathways involved in microbiota regulation are activated through nod-like receptors (NLRs), cytoplasmic sensors of cellular and tissue stress. Mice lacking *Nlrp3*, *Nlrp6*, or other inflammasome components, exhibit an "inflammasome-mediated dysbiosis," characterized by *Prevotellacea* and TM7 over-representation, increased expression of pro-inflammatory cytokines, increased experimental colitis severity and an autoimmune-like response.[90,91] Other immunity-driven mechanisms seem to be involved in gut dysbiosis, such as the dysregulated production of antimicrobial peptides by Paneth cells in intestinal crypts, which can lead to microbiota shifts and colonization of physiologically sterile inner mucus layers.[52,92] Together, these findings suggest that NLRP3 inflammasome bioactivity is crucial to maintaining gut homeostasis.

7. An Experimental Framework to Test the Proposed Hypothesis

The hypothesis presented relies on a causal role of the gut microbiota in the development of depressive symptomatology and co-morbid systemic conditions via its influence on inflammatory processes.

The mainexperimental frameworkto test thishypothesiswould involve large-scale studies investigating gut microbiota composition in depressed patients with orwithout co-morbid illnesses, and healthycontrols, toidentify bacterial familiesand/orspecieswhich are consistently altered in those conditions. Inflammatory biomarkers screening could be performed to investigate the possibility that a causal correlation exists between gut microbiota composition and dysregulated immune processes in MDD and comorbid systemic illnesses. This could help identify immune mediators and pathways driving MGIB axis dysregulation, which may play a causal role in the development of depressive symptoms and co-morbid systemic conditions. Further, such studies could profile the gut metabolome aiming at identifying consistent metabolites, which might modulate the inflammatory status underlying these conditions.

Those studies could identify bacterial families and/or species, which are driving the inflammatory changes observed in MDD. This could demonstrate that a causal relationship exists between shifts in gut microbiota composition, and inflammatory changes, leading to depressive symptoms onset and co-morbid systemic illnesses.

If bacterial species and/or families driving MDD symptoms are successfully identified, their abundance could be therapeutically modulated to decrease pro-inflammatory signaling and obtain antidepressant effects, while ameliorating co-morbid condition(s) (if present).

Such modulation could be obtained via approaches that alter gut microbiota composition, such as fecal microbiota transplantation (FMT, the transfer of fecal material from a healthy donor to restore gut microflora biodiversity) or introduction of specific bacterial species. An indirect approach could involve the pharmacological inhibition of specific immune mediators, which determine the abundance of specific bacterial clades. Other avenues to alter the representation of bacterial clades could involve psychobiotics (probiotics and prebiotics) supplementation and diet (see section 8.3 below).

8. How Can We Leverage the MGIB Axis in the Treatment of MDD?

The MGIB axis could represent a valuable therapeutic target for MDD treatment via modulating NLRP3 activity and gut microbiome composition. Fluoxetine, a commonly used antidepressant, inhibits NLRP3 inflammasome activation.[82] An alternative or adjunct approach to such prototypical antidepressant pharmaceutical treatment would be to manipulate the gut microbiome, to reduce NLRP3 inflammasome bioactivity and increase the abundance of species with immunoregulatory and anti-inflammatory properties.[93–95]

8.1. NLRP3 Inflammasome Modulation

A randomized controlled trial (RCT) investigating minocycline augmentation for MDD reported improvements in several measures, including global impression, functioning, and quality of life.[96] However, the primary outcome measure (Montgomery–Asberg Depression Rating Scale) was unaffected.[96] Other RCT have investigated anti-inflammatory augmentation in MDD, and found increased efficacy and decreased latency of antidepressant effects onset.[97–99] A RCT investigating TNF inhibition in MDD found that only patients with dysregulated inflammatory profiles benefit from such therapy, raising the possibility that increased NLRP3 baseline activity might be a treatment response predictor.[100] When designing NLRP3-directed therapies, it is important to consider the potential effects on physiological immune responses, whose functionality needs to be preserved.

8.2. Fecal Microbiota Transplantation

Anecdotal and indirect evidence of mood enhancing and antiinflammatory effects of FMT are available from IBD, *Clostridium difficile* infection and Crohn's disease patients undergoing such procedures.[94] Accordingly, pre-clinical studies have shown the transmissibility of gut microbiota-driven behaviors.[10,39] Although no study has investigated the reversed approach (e.g., FMT from healthy donors to depressed recipients), the transmissibility of microbiota-associated behaviors suggests that FMT might prove

valuable in treating MDD.[10,39] When designing FMT-related therapies, it is fundamental to maximize safety, while considering potential short- and long-term adverse effects.[101]

8.3. Psychobiotics

Probiotics are bacteria that yield beneficial health outcomes, while prebiotics are compounds that produce changes in gut bacteria composition and/or function.[102] Psychobiotics are probiotics and prebiotics that positively affect mental health and can ameliorate psychiatric symptoms.[93,103–107] Clinical trials involving psychobiotics administration are sparse but on the rise, and are yielding promising results (Table 2).

In a study with treatment resistant MDD patients, 8 weeks supplementation with *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Streptoccocus thermophiles* and magnesium orotate reduced depression scores and improved life quality.[108] Similarly, the administration of *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* decreased depression scores, and high sensitivity CRP, while increasing glutathione levels.[109] A RCT investigating 6 weeks supplementation with *Bifidobacterium longum* in IBS patients reported decreased depression scores and increased life quality.[110] Although this study has been challenged for its intrinsic low *fragility index* (an index of robustness of clinical trials outcome), imaging investigations uncovered attenuated amygdala and temporal activation in response to fearful stimuli correlated with IBS symptoms amelioration.[110,111] Similarly, a cocktail of *Bifidobacterium animalis* subsp. *lactis*, *Streptococcus thermophiles*, *Lactobacillus bulgaricus*, and *Lactococcus lactis* subsp. *lactis* decreased neural activity in negative emotion- and sensation-processing brain areas in healthy women.[74] This suggests that introducing commensal bacteria to the gut can have profound influences on region-specific brain activity. The identification of such effects represents an important step toward using psychobiotic supplementation for conditions that alter brain activity, such as MDD.[110,112] Accordingly, *Bifidobacterium longum* administration in healthy volunteers increased prefrontal cortex activity and decreased daily stress levels, while attenuating cortisol and anxiety responses to a stressor.[113] Similarly, *Lactobacillus Rhamnosus* supplementation in pregnancy and postpartum reduced the prevalence of post-natal depression and anxiety symptoms.[114]

An important challenge in psychobiotics research is the identification of bacterial strains with consistent efficacy. For example, in one study, healthy volunteers dosed for 30 days with *Lactobacillus helveticus* and *Bifidobacterium longum* displayed decreased anxiety and cortisol levels compared to baseline, while in another study, 21 days of treatment did not affect psychological symptoms.[105,115] Two other studies reported that *Lactobacillus casei* Shirota improved mood in healthy subjects with low baseline mood score, and decreased anxiety scores in chronic fatigue syndrome patients.[116,117] Interestingly, gut *Lactobacillus* and *Bifidobacteria* representation was increased in a chronic fatigue syndrome cohort following supplementation, suggesting that effective psychobiotic treatment might have a “ripple effect” (the effects on overall gut balances) on gut microbiota composition.[117] More recently, the use of a “parapsychobiotic” (an inactivated psychobiotic) containing *Lactobacillus gasseri*, was shown to prevent the rise in stress-responsive microRNAs and cortisol, while improving sleep quality and bowel habits in chronically stressed students.[118]

8.4. Diet

Diet has a potent influence on gut microbiome composition and function.[119] Depressive symptoms prompt the consumption of foods high in sugar and saturated fats, driving gut dysbiosis and compounding depressive symptoms. Not surprisingly, western diet (high fat, high sugar content) increases intestinal permeability and pro-inflammatory signaling.[120] However, by stimulating the production of immunomodulatory compounds, such as SCFAs, a diet rich in fibre, for example, should be considered as an adjunct therapy for MDD.[95] Indeed, MDD patients who consume fermented milk products had increased levels of *Bifidobacterium*, a genus that is reduced in MDD patients.[121]

9. Conclusions and Outlook

The evidence for an involvement of NLRP3-mediated pathways in the cross-talk networks linking the gut microbiota, the immune system and the brain, is compelling. The microbiota-inflammasome hypothesis of MDD presented here suggests that NLRP3 signaling triggered by psychological stress affects anxiety and depressive-like behaviors while altering gut microbiota composition and accommodating an expansion ofbacterial species which have pro-inflammatory effects. This results in decreased levels of available monoamines and neuroactive compounds while fueling gut dysbiosis and increasing the risk for NLRP3-driven co-morbid illnesses. Conversely, chronic stress results inimmune balances disruption that can trigger dysbiotic states which fuel systemic low-grade inflammation, increasing the susceptibility to co-morbid systemic illnesses.

The potential causal role of the gut microbiota in the development of MDD and co-morbid conditions needs further investigation; this could shed light on the pathophysiological events leading to MDD onset and the development of co-morbid systemic illnesses. New therapeutic strategies might target the MGIBaxis, either through direct NLRP3 inhibition, orthroughgut microbiota remodelling. The latter could involve using psychobiotics, fecal microbiota transplantation, or dietary changes to decrease NLRP3 inflammasome signaling and neurodegeneration. While these approaches offer exciting opportunities for novel therapies, further pre-clinical and clinical research are required to translate their potential into clinical practice.

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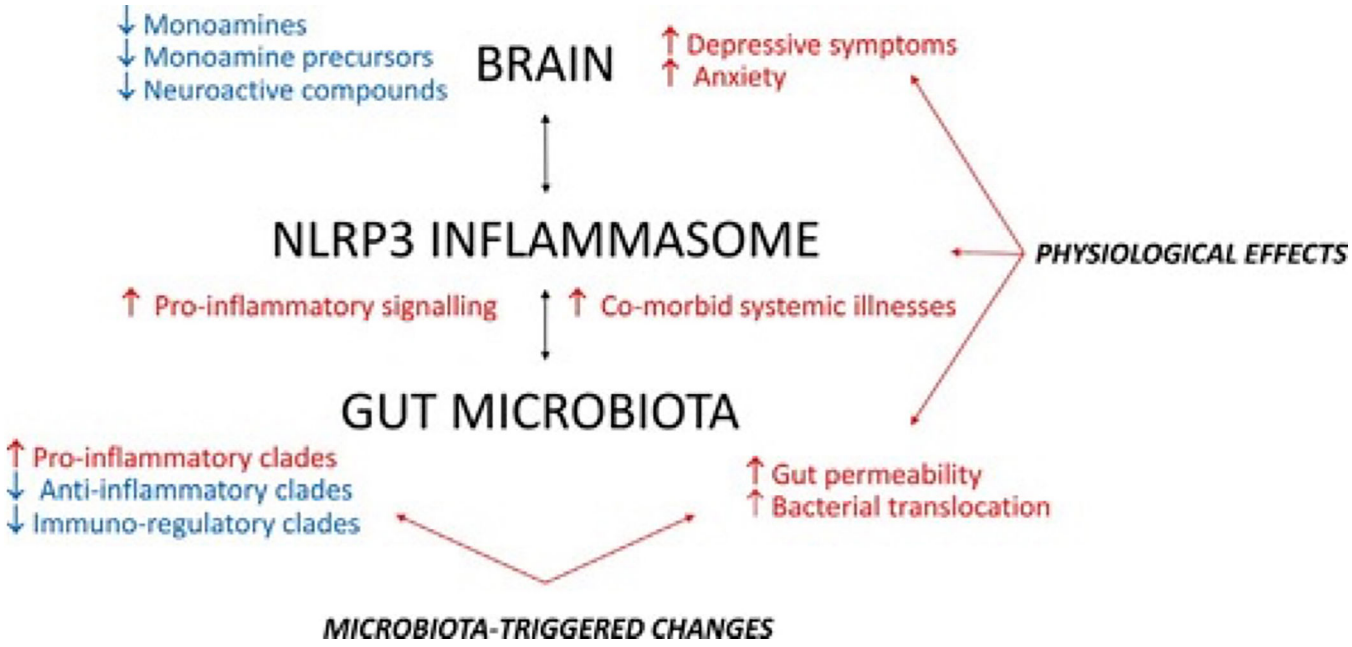

Figure 1.

The microbiome-inflammasome hypothesis of major depression and co-morbid systemic illnesses. Psychological stress exposure increases NLRP3 signaling, that increases anxiety- and depressive-like behaviors. Stress-associated gut microbiome changes mediated by the NLRP3 inflammasome and IL1B pathways affect anxiety- and depression-like behaviors and increase the likelihood of developing co-morbid systemic conditions. This is mediated by: 1) increased representation of pro-inflammatory bacterial clades; 2) decreased representation of anti-inflammatory and immunoregulatory bacterial clades; 3) altered bioavailability of monoamine precursors and neuroactive compounds produced by the gut microbiome; and 4) alterations in intestinal structural integrity (e.g., leaky gut), which result in the translocation of bacteria and by-products in physiologically sterile bodily compartments, fuelling pro-inflammatory signaling.

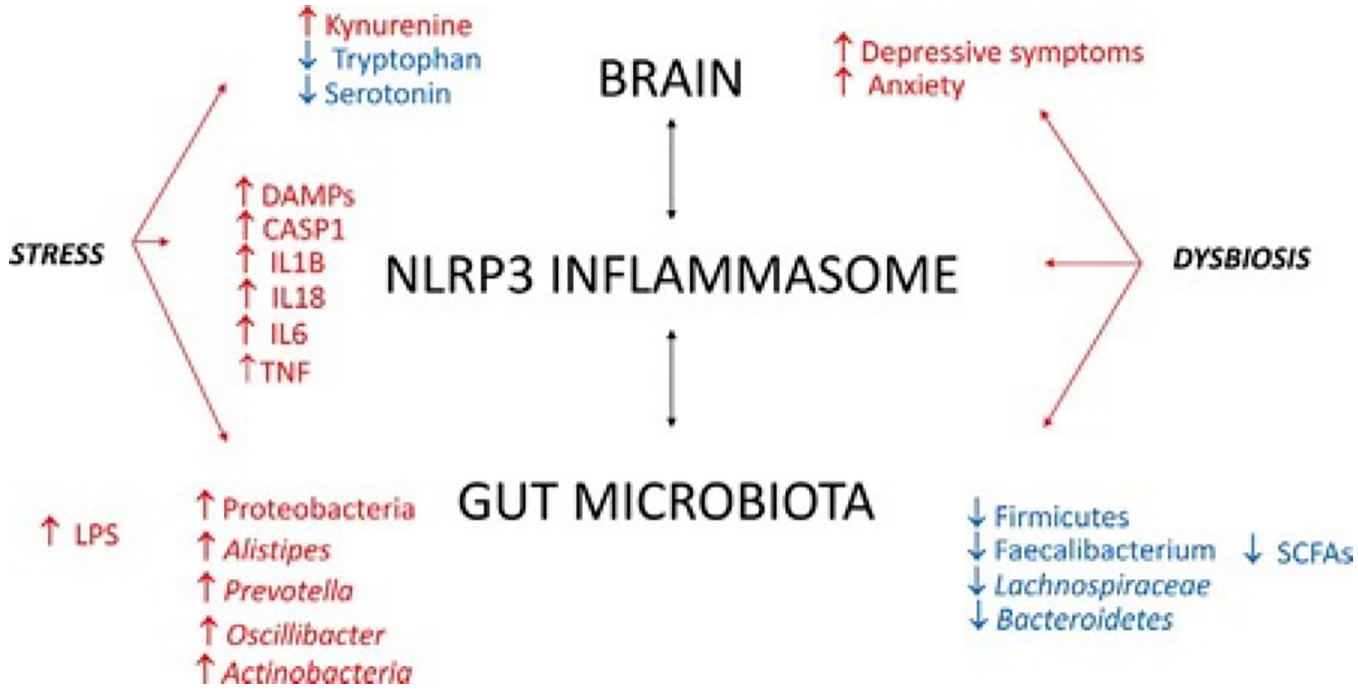

Figure 2.

Molecular links connecting the microbiome-inflammasome hypothesis of major depression and co-morbid systemic illnesses. Psychological stress exposure increases pro-inflammatory signaling (e.g., NLRP3, IL1B, IL18, IL6, TNF). This heightened inflammatory state decreases the availability of neurotransmitters (e.g., serotonin) and their precursors (i.e., tryptophan) and increases the turnover of neuro-transmitters (e.g., increased kynurenine), leading to anxiety- and depressive-like behaviors. Such heightened inflammatory status increases the likelihood of co-morbid conditions. At the same time, increased pro-inflammatory signaling modulates gut microbiota composition, increasing the representation of bacterial clades conducive to pro-inflammatory signaling (e.g., *Proteobacteria, Allistipes, Prevotella, Oscillibacter, Actinobacteria*) and decreasing the representation of bacterial clades conducive to anti-inflammatory signaling (e.g., Firmicutes, Faecalibacterium, *Lachnospiraceae*, *Bacteroidetes*). At the same time, gut dysbiosis caused by intestinal and co-morbid conditions increases pro-inflammatory signaling via increasing the representation of pro-inflammatory bacterial clades, which increases the production of LPS and other bacterial toxins and decreases the production of microbiota-produced anti-inflammatory compounds (e.g., SCFA). Such shifts in gut microbiota composition increase the likelihood of developing MDD and other mental illnesses.

Table 1.

Summary of studies reporting increased and decreased levels of bacterial families in MDD patients.

Increased in MDD	Decreased in MDD	Reference
Firmicutes Actinobacteria Lachnospiracea	Bacteroidetes Proteobacteria	[36]
Actinobacteria (females only)	Bacteroidetes (males only)	[38]
Bacteroidetes *Bacteroides* *Prevotella* *Paraprevotella*	Firmicutes *Lachnospiracea incertae sedis* *Coprococcus* *Clostridium IX*	[26]
Actinomycineae Coriobacterineae Coriobacterineae Lactobacillaceae Streptococcaceae Clostridiales *Eubacteriaceae* *Lachnospiraceae* *Ruminococcaceae* *Erysipelotrichacea*	 Bacteroidaceae Lachnospiraceae Acidaminococcaceae Veillonellaceae *Sutterellaceae*	[10]
Thermoanaerobacteriaceae	Prevotellaceae	[39]
	Bifidobacterium *Lactobacillus*	[121]
Enterobacteriaceae *Alistipes* Acidaminococcaceae Fusobacteriaceae Porphyromonadaceae Rikenellacea	Bacteroidaceae Erysipelotrichaceae Lachnospiraceae Prevotellaceae Ruminococcacea Veillonellaceae	[27]

Table 2.

Summary of clinical studies reporting biological and/or mood outcomes following psychobiotics supplementation.

Bacterial strain	Condition	Probiotic treatment	Mood effects	Biological effects	Reference
Lactobacillus rhamnosus HN001	Pregnant women	150–330 days	Reduced post-natal depression scores Reduced anxiety	None investigated	[114]
Bifidobacterium longum NCC3001	Irritable bowel syndrome	42 days	Decreased depression scores Increased quality of life Amelioration in general physical health Amelioration in problems with work or other daily activities	No difference in serum inflammatory markers No changes in gut microbiome composition *Bifidobacterium longum* detected in 80% of treated patients at end of treatment Reduced amygdala and frontal and temporal cortices engagement in response to fearful stimuli (correlated to IBS symptoms relief) Heightened occipital regions engagement in response to fearful stimuli	[110]
Lactobacillus helveticus Bifidobacterium longum	Low mood	56 days	None found	High levels of baseline vitamin D predicted better treatment response	[122]
Lactobacillus acidophilus Bifidobacterium bifidum Streptoccocus thermophiles	SSRI treatment resistant depression	56 days	Decreased depression scores Improved quality of life	None tested Hypothesized intestinal anti-inflammatory effects	[108]
Lactobacillus gasseri CP2305 (inactivated)	Stressed students	84 days	Improved sleep quality Decreased stress levels	Improved sleep electroencephalogram Prevented increases in basal cortisol levels Prevented increases in expression of stress-responsive microRNA miR-144 (females only) Normalized bowel habits	[118]
Lactobacillus acidophilus Lactobacillus casei Bifidobacterium bifidum	Major depressive disorder	56 days	Decreased depression scores	Decreased insulin levels Decreased hsCRP levels Increased glutathione levels	[109]
Bifidobacterium longum 1714	Healthy subjects	28 days	Decreased daily stress levels Decreased anxiety response to a stressor	Improved visuospatial memory Decreased cortisol response to a stressor Enhanced prefrontal cortex activity	[113]
Bifidobacterium bifidum W23 *Bifidobacterium lactis* W52 *Lactobacillus acidophilus* W37 *Lactobacillus brevis* W63 *Lactobacillus casei* W56 *Lactobacillus salivarius* W24 *Lactococcus lactis* (W19 and W58)	Healthy subjects	28 days	Reduced rumination Reduced aggressive thoughts	None investigated	[123]
Lactobacillus acidophilus LA5 and *Bifidobacterium lactis* BB12 (GROUP 1) *Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Streptoccocus thermophilus* (GROUP 2)	Healthy subjects	42 days	Decreased anxiety scores Decreased depression scores	Improved general health	[124]
Bifidobacterium animalis subsp lactis I-2494 *Lactobacillus bulgaricus* I–1632 and I-1519	Healthy subjects	28 days	None investigated	Altered activity of interoceptive and somatosensory regions Decreased activity of mid insula cortex and primary somatosensory	[74]

Bacterial strain	Condition	Probiotic treatment	Mood effects	Biological effects	Reference
Lactococcus lactis subsp lactis I-1631				cortex Decraesed activity of frontal, prefrontal, and temporal cortices, parahippocampal gyrus, and the periaqueductal gray	
Lactobacillus helveticus R0052 *Bifidobacterium longum* R0175	Healthy subjects	30 days	Decreased scores of somatisation, depression and anger–hostility	None investigated	[105]
Lactobacillus casei Shirota	Healthy subjects	20 days	Patients more depressed at baseline reported improved mood	None investigated	[116]