Inflammatory processes have been linked to depressive illness, possibly being driven by stressful experiences. As well changes in the balance between microbial species compromising the microbiome could be important in precipitating cytokines and other inflammatory factors that, in turn, influence several pathways leading to depression. In particular, hormonal (e.g. glucocorticoids), trophic (e.g. reductions of growth factors) and oxidative stress signaling in the brain can be altered by the inflammatory milieu, including excessive cytokine release, which contribute to the symptoms that characterize a depressed state (e.g. anhedonia, lethargy, disturbed feeding). Identifying the ‘signature’ of inflammatory changes evident in the microbiome of specific depressed patients could yield important biomarkers to guide the development of personalized approaches to treatment.

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Inflammatory process are believed to contribute to a variety of illnesses, including metabolic syndrome, diabetes and heart disease [1,2]. Aside from these conditions, which are among the most pernicious world-wide, inflammatory process have also been linked to poor recovery from stroke [3] and neurodegenerative disorders [4]. As well, there has been ever increasing evidence pointing to a role for inflammatory processes in psychological disorders, such as depressive illnesses [5], and might contribute to the comorbidity that is frequently apparent between depression and other conditions [6,7]. Excessive pro-inflammatory cytokine levels, or a failure of inflammation resolving appropriately, are thought to be key in the evolution of such disturbances, and thus appreciable efforts are being made to define the processes associated with persistent inflammation, with the goal of facilitating approaches to delay the onset and progression of illnesses [8]. In this regard, appreciable efforts are being made to identify biomarkers related to inflammation and other processes that might signal disorders [9], as well as inflammatory biomarkers that might be predictive of therapeutic responses to antidepressant agents [10]. Indeed, the frequent failures to attenuate depression using standard antidepressant medications (e.g., SSRIs) might stem from persistent inflammatory activation [11**].

Evidence tying inflammatory processes to depressive illnesses

The confluence of several independent lines of evidence has provided increasing support for the position that inflammatory factors are causally linked to depressive illnesses. Genome-wide association and differential gene expression in transcriptomic studies using tissue from depressed humans or stressed rodents revealed over-representation of genes related to immune system functioning and the inflammatory response [12]. Moreover, depression was accompanied by elevated circulating cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), as well as acute phase proteins (e.g., C-reactive protein) and were especially notable when depressed symptoms included suicidal ideation [13]. Likewise, the anhedonia (reflected by reduced sucrose consumption) elicited by a chronic mild stressor regimen in rodents, was accompanied by increased up-regulated IL-1β and IL-6 expression in the hippocampus and prefrontal cortex, together with markers of microglia activation, and each of these effects was attenuated by antidepressant treatments [14]. Collectively, these studies raise the possibility that genetic (as well as proteomic) indices of cytokines or circulating cytokines themselves could offer viable biomarkers to facilitate diagnosis, treatments, and perhaps recurrence of depressive disorders [15]. Yet, it was also recognized that numerous factors, such as sleep problems, associated with depression, might be responsible for the cytokine changes [16].

Various treatments (e.g., endotoxin administration) that promoted inflammation elicited a constellation of symptoms, including anhedonia, in animal models of the disorder [17] and induced signs of depression in humans [11**]. There were also several reports indicating that anti-inflammatory agents (e.g., aspirin or the NSAID celecoxib), may bolster the impact of SSRI treatments in humans and in animal models of the illness [18]. Although such effects were not always apparent, a meta-analysis indicated that celecoxib acted as a positive adjunctive treatment [19] and another found that
treatment resistance was most likely to occur among patients who displayed persistently elevated TNF-α [20]. Intriguingly, ‘traditional’ antidepressants themselves might have anti-inflammatory properties, as the SSRI, fluoxetine, and the tricyclic agent, imipramine, produced a reduction IL-6 and IFN-α mRNA expression, while increasing that of the anti-inflammatory IL-4 within the hypothalamus [21].

Strong evidence supporting a cytokine-depression link have come from studies showing that interferon-α (IFN-α) administration in treating hepatitis C and malignant melanoma, frequently induced marked depressive symptoms in many patients, especially those with preexisting symptoms, women with a history of depression or in individuals with high circulating IL-6 [22]. Importantly, in some instances these effects could be attenuated by treatment with antidepressant agents, such as escitalopram [23], and a meta-analysis suggested that antidepressants were moderately effective prophylactic treatments [24]. As strong as these data were, it should be considered that patients in these studies were likely undergoing some distress, and there is reason to believe that stressors and cytokine treatments can have synergistic actions on cytokine and neurochemical functioning, as well as on signs of depression [25].

**Inflammatory changes in brain and depression**

While not denying the possible role of peripheral cytokines, brain cytokine variations (or downstream effects of the cytokine alterations) are likely fundamental in depression. In this regard, cytokines are produced by microglia (e.g., in the hypothalamus, hippocampus and prefrontal cortex) in response to neuronal injury, immune challenge and in response to a variety of environmental stressors. These cytokines could influence depression through inhibition of growth factors (e.g., brain derived neurotrophic factors; BDNF) or the production of toxic metabolites related to aberrant neurotransmission [26]. Indeed, these cytokines can give rise to the production of neurotoxic compounds, such as quinolinic acid, and the consequent neuronal destruction could be responsible for the symptoms of depression. Likewise, activated microglia could stimulate excitotoxic or pro-oxidative processes, including increased glutamate activity, which favor cell loss and the resultant depression [27,5].

**Links between the microbiome, cytokines and depression**

Microorganisms that inhabit the gastrointestinal tract share reciprocal connections with the host immune system and can influence neurodevelopment and affect psychological processes [28**]. Increasing evidence has pointed to the involvement of gut bacteria (microbiome) and in particular, its substantial inflammatory milieu, in the induction of depressive illnesses [28**]. Germ-free mice (born and raised in a sterile environment) displayed immune disturbances, including defective microglia that could be restored by later colonization with commensal bacteria [29**]. In line with the view that the microbiome might have immunoregulatory properties, supplementation with probiotic bacteria reduced intestinal markers of inflammation in animal models of colitis [30] and attenuated sickness behaviors that were engendered circulating cytokine levels and microglial activation in a mouse model of liver inflammation [31]. Likewise, cytokine elevations within the frontal cortex elicited by the bacterial endotoxin lipopolysaccharide (LPS) were prevented in mice fed with a diet rich in prebiotics that comprise non-digestible fibers that promote gut microbial growth [32**].

**Implication of microbiota in inflammatory response to stressors**

Gut bacterial communities are sensitive to a variety of challenges, including stressors [33**,34,35**]. In addition to their role in pathogen-driven inflammation, gut bacteria might also contribute to immune activation that occurs in sterile conditions. In fact enhanced splenic macrophage reactivity elicited by a social stressor was prevented in antibiotic-treated and germ-free mice [36], and prebiotics attenuated anxiety and colonicmicrobiota alterations associated with stressors [35]. Moreover, inactivation of gut-derived LPS (found in the outer membrane of gram-negative bacteria), attenuated plasma and brain cytokine elevations ordinarily induced by an acute stressor [37,38], suggesting that this microbial product (and downstream cytokine signaling via Toll-like receptor 4) was required for the stressor-provoked cytokine changes.

**Microbiota–gut–brain axis and links with stress-related disorders**

Germ-free and antibiotic-treated mice exhibit several anxiety-like and depressive-like phenotypes, as well as alterations of neurotransmitters and of their receptors (e.g., 5-HT, GABA receptor subunits), neuroendocrine factors (e.g., CRH), and neurotrophins (e.g., BDNF) [39,40]. Further indications of microbiota influence on brain processes and behaviors have come from reports showing that probiotics attenuated anxiety-like and depressive-like behaviors and limited plasma corticosterone elevations and IL-10 reductions as well as the hippocampal monoamine (5-HT and NE) reductions elicited by a chronic restraint stressor in rats [41]. Probiotics also prevented impairments of neurogenesis and BDNF changes elicited by stressors [42].

Increased permeability of the blood-brain barrier (BBB) and altered expression of tight junction proteins were reported in germ-free mice, and colonization with microbiota from conventionally raised mice partially reversed this deficit [43*]. These findings raise the possibility that
microbiota alterations may facilitate the passage of circulating molecules that could not have infiltrated (e.g., cytokines, bacterial metabolites) the brain and promote their interactions with neurochemical factors.

**Microbiota in clinical depression**

Although reports are scant, it was shown that depressed individuals had more bacteria from the *Proteobacteria* and *Actinobacteria* phyla and in the *Alistipes* genus, as well as decreased levels of several genera of the *Firmicutes* phylum. Moreover, changes in the *Faecalibacterium* genus were negatively correlated to depression severity, whereas *Faecalibacterium* over-representation in healthy control relative to depressed subjects [44] possibly reflecting a protective effect against depression through anti-inflammatory processes. Despite the limited clinical data available in this regard, probiotics were reported to diminish psychological distress, and prebiotics similarly modified the cortisol awakening response (which is increased in individuals at risk for depression) and reduced attentional vigilance for negative versus positive stimuli (reflective of an anxiolytic profile) [45]. The observation that probiotics reduced plasma cytokine levels among individuals suffering from inflammatory conditions and attenuated mitogen-stimulated cytokine elevations in healthy participants [46] and that among elderly participants prebiotics decreased circulating immune markers such as IL-1β, while increasing IL-10 and natural killer cell activity [47], suggests that the positive effects of these microbiota-targeting compounds on mood states could be linked to their actions on immune processes.

**Microbial changes in relation to early life or prenatal stressors**

Environmental challenges faced early or late in life could have dramatic consequences, especially in the face of a compromised BBB stemming from developmental effects of an imbalanced microbiota. In fact, maternal prenatal stressor experiences were linked to a greater abundance of Proteobacterial groups that contain pathogens (e.g., those related to *Escherichia*, *Serratia*, and *Enterobacter*) [48]. As well, consistent with the view that associations between microbiota and temperament could be initiated early in life, it was reported that among children of about 2 years of age, bacterial diversity was linked to temperament and certain bacteria were positively correlated with sociability and activity levels [49]. Preclinical studies likewise demonstrated that microbiota alterations that occurred early in life modulated subsequent brain development [50] and proactively influenced physical and mental health in adulthood [34,51**].

**Summary**

There is ample evidence indicating that qualitative, and most likely quantitative, changes in the nature of the species comprising the microbiome can have dramatic long term consequences on the brain–immune axis. As depicted in Figure 1, Psychological, immunological and chemical stressors serve to shape the inflammatory milieu within the gut, and depending upon the severity and timing of such insults, could adversely influence brain–immune communication, including hormonal, neurotransmitter, cytokine and other growth factor processes, and hence favor the evolution of depressive symptomatology (especially vegetative elements of the illness). The recent promotion of individualized treatments of depression, like that of other disease conditions, might contribute to better treatments of first episode depression and may provide targets that diminish illness recurrence, which is notoriously high. Cytokine biomarkers have been proposed as being important in this regard, and it may be useful to include research that focuses on microbiome alterations in developing treatment strategies.

**Conflict of interest statement**

Nothing declared.
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References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:
 ● of special interest
 ● of outstanding interest


This review describes how the innate and adaptive immune systems interact with neurobiological systems, resulting in elevated risk for depression. Moreover, those instances of depression that are provoked by inflammatory processes may contribute to non-responsiveness to current antidepressant therapies.


This study suggests that among germ-free mice, brain microglia and immune functioning are compromised. Likewise, when microbiota complexity was diminished, their functioning was impaired, but this could be reversed through colonization with a complex microbiota. It appeared that short-chain fatty acids, microbiota-derived bacterial fermentation products, served to maintain microbial homeostasis.


This is the first among several studies showing that an intervention directly targeting commensal bacteria (in the form of prebiotics) attenuates sickness behaviors and brain cytokine elevations normally elicited by an immunogenic challenge.


This study shows that disturbed brain functioning may stem from altered immunoregulatory responses and shifts in gut microbiota composition. The view was taken that a dysbiotic state and the presence of particular microbial markers may be aligned with the impact of strong stressors on cognitive functioning. As well, this study points to novel pathways by which microbiota influence brain processes, and as such might serve as targets for pharmacological therapy.


This study demonstrated that the gut microbiota regulate the blood-brain barrier permeability from early life to adulthood and thus plays a key role in the protection of the brain throughout life.


This paper is of particular interest in that it suggests that not only immunological and physical, but psychologically relevant stressors that occur at early developmental times may have long-term behavioural consequences that are related to the state of the microbiota. The implication is that the nature of intestinal microbial species may be programmed by early life stressor exposure and later foster the development of anxiety-like behavior.