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The Brain-Immune-Gut Triangle: Innate Immunity in Psychiatric and Neurological Disorders

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Abstract: The communication between the immune and central nervous systems has been known for decades. Although the biological rules and complexity of the neuroimmune axis is yet to be clarified, in the modern era of immunology and clinical neurosciences it has become a dynamically evolving paradigm. In this review we trace the major findings of this emerging field with a special focus on innate immune cells and their phylogenetically conserved receptors, in line with their role in various psychiatric and neurological diseases. A particular interest will be given to monocytes, macrophages/microglia, dendritic cells, Toll-like and RIG-I-like receptors as well as their contribution to inflammation and other pathological processes in the CNS. Uncovering immunological mechanisms in the context of brain functions emerges as a promising avenue for future therapeutic interventions in various, still incurable ailments such as Alzheimer's disease, schizophrenia, or different mood disorders such as major depression or bipolar disorder. We propose new perspectives for the pharmacological modification of innate immune cells and their response to inflammatory cues in the brain. A holistic concept of studying the gut-brain-immune triangle is also suggested to bring up novel approaches in immunology, gastroenterology, psychiatry and neurology.

Keywords: Gut microbiota, gut-brain axis, innate immunity, neuroimmunology, pattern recognition receptors, psychoneuroimmunology.

INTRODUCTION

The old concept that the three major systems of the body – the immune, the endocrine, and the nervous system – communicate with each other was established after a long period of continuous scientific observations, which finally gave rise to the field of psychoneuroimmunology more than three decades ago. In 1980 Robert Ader coined the term '*psychoneuroimmunology'* (PNI) to grasp the idea of convergent findings showing the inter-communicative nature of the brain and the immune system. This new field emerged as an integrative discipline trying to shed light on processes by which mental events modulate immune functions and how, in turn the immune system is able to alter or interfere with the function of the mind [1]. However, this modern period of psychoimmunological or psychosomatic research was preceded by accidental observations or purposeful investigations carried out through many centuries. The historical antecedents root in as old tradition of the ancient tenets of Chinese, Indian, and Greek natural philosophies [2, 3].

The foundation stones of modern PNI theory were laid in the middle eighties when Besedovsky and colleagues showed that glucocorticoid serum levels are elevated in the course of immune responses to innocuous antigens. This phenomenon seemed to influence the capacity of the immune system to respond to additional challenges, since the increase in corticosterone levels during the response to an antigen interfered with the response to a '*second unrelated'* one [4]. This observation also provided evidence for the communication between the immune and neuroendocrine systems by demonstrating that supernatants of activated immune cell cultures contained factors capable of stimulating the hypothalamic-pituitary-adrenal (HPA) axis [5]. It was also reported that glucocorticoids influenced the production of interleukin-2 (IL-2), an essential growth factor of T-lymphocyte proliferation, and other soluble factors [6]. Resting immune cells were shown to be less sensitive to this inhibitory glucocorticoid-mediated effect than activated ones. Thus, the immune-HPA circuit was proposed as an important regulatory network involved in fine tuning immune responses. Interleukin-1 (IL-1) was the first cytokine that was shown to have the potential to stimulate the HPA axis [7], and soon after this observation many other chemokines, cytokines and growth factors including IL-8, IL-6, tumor necrosis factor- α (TNF-α), interferon-γ (IFNγ), IL-12, and granulocyte macrophage-colony stimulating factor (GM-CSF) also turned out to possess this capability [8-10]. These early evidences showed that the immune system is able to elicit neuroendocrine responses, thus it was claimed to be a '*peripheral receptor organ*' or a '*sixth sense*' that transmits information to the brain about endogenous/exogenous stimuli [4, 11]. Also at this time, Blalock and Smith discovered a bidirectional communication pathway between the immune and neuroendocrine systems in which immune cells can produce pituitary peptide hormones. Since brain cells can also produce cytokines and other soluble mediators it became obvious that the common use of ligands and receptors shared by the two systems may occur [12].

A decade later the rapid increase of new findings broadened the spectrum of our knowledge within the field of PNI. Significant discoveries showed that endogenous

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catecholamines can selectively suppress $CD4^+$ helper T-cell (Th1)-mediated inflammation and can protect the host from deleterious effects of inflammatory cytokines produced by innate immune cells [13]. A link between catecholamines and glucocorticoids acting as synergistic factors was also established [13, 14] and it also became clear that several cytokines can induce profound changes in cognition and behavior. Some of these effects turned out to be under the control of catecholaminergic and serotonergic neurons of the central nervous system (CNS) [15, 16]. Recently, the critical role of the immune-HPA axis in controlling inflammatory and autoimmune diseases also became evident. A decent amount of experimental and clinical evidence underscored the relevance of this feed-back mechanism during both infectious and autoimmune disorders [17, 18]. As Sternberg argues in a recent review, the CNS can be considered as an integral part of the innate immune system by affecting immune responses [18]. The stress response mediated by the neuroendocrine and the sympathetic/parasympathetic nervous systems generally exerts a marked inhibitory effect on systemic innate immune responses, while modulation through the peripheral nerves amplifies local innate immune responses. The main role of this integrated entity is to first amplify local innate inflammatory and systemic acute-phase responses in order to eliminate invading pathogens, and subsequently terminate inflammation and restore host homeostasis [18].

Contemporary psychoneuroimmunology is distinguished from its ancestors by its novel methodology and theoretical design. Early neuroimmunologists considered the immune and nervous systems as separate parts, but a crucial conceptual leap led to the emergence of the modern approach. This new concept represents neuroimmune communication as an integrated physiological entity with the immune and nervous systems being its two aspects [19]. Recently, a third element has also been added to the big picture. According to a considerable number of recent reports the gut microbiota has a great impact on the development and overall physiology of the brain and the immune system [20-23]. Thus the intestinal microflora – under the control of brain-affected immune surveillance – readily fits into the tripartite-like functional and regulatory network of gut-brain-immune communication. These new findings enable us to take an important step towards a more holistic view of the *'brain-immune-gut triangle'* (BIG-T) acting as a dynamic functional unity.

THE INNATE IMMUNE SYSTEM AND ITS ROLE IN VARIOUS CNS PATHOLOGIES

The innate immune system represents the most ancient host defense mechanism against invading pathogens. Elements of this system use germline-encoded pattern recognition receptors (PRRs) to detect pathogen-associated molecular patterns (PAMPs), which involve evolutionally conserved foreign motifs expressed by big families of microbes. Innate immune cells provide us with the first line of defense if the natural physical and chemical barriers of the body, i.e. the skin and the mucosa have failed to stop them [24]. Innate recognition by PRRs leads to nuclear factor kappa-b (NF-κB)-mediated inflammatory, chemokine, and/or type I interferon (IFN) responses depending on the nature of the invading organism. The families of PRRs identified so far include membrane-bound Toll-like (TLRs), C-type lectin (CLRs), and cytosolic nucleotide-binding oligomerization domain containing (NOD)-like, absent in melanoma 2 (AIM2)-like, and retinoic acid inducible gene 1 (RIG-I)-like receptors (RLRs) [25-29]. Intracellular endosomal TLRs together with RLRs and other cytoplasmic sensors can detect the nucleic acid motifs of intracellular pathogens, such as the genome or replication intermediates of viruses, and initiate the secretion of type I IFNs in many cell types of the body [30-33]. Cell surface TLRs on the other hand preferentially recognize essential cell wall components of bacteria or fungi [34-36]. Although the expression of PRRs is not restricted to immune cells, professional antigen-presenting cells (APCs), such as B-lymphocytes, dendritic cells (DCs) and macrophages possess the broadest repertoire [33, 37, 38]. The production of proinflammatory cytokines (IL-1β, IL-6, TNF-α) in the tissue environment of resident DCs and macrophages subsequent to innate recognition offers an important mechanism in first line of defense. Furthermore, certain PRRs also sense host-derived '*self*' material that may become available during cellular or tissue injury. These endogenous PRR ligands have been termed '*damage-associated molecular patterns*' (DAMPs) having the potential to elicit inflammation and cell death by activating innate receptors, although their role in immune homeostasis is yet to be elucidated [39]. Chronic inflammation provoked either by endogenous or exogenous stimuli leads to significant tissue damage and may develop to autoimmune processes [40, 41]. Thus, the innate immune system thought to play an important role in the etiology of autoimmune diseases as an initiator and sustainer of the process leading to autoinflammatory diseases, or by triggering long-term adaptive immune responses against self structures in '*classical*' autoimmune diseases [42, 43].

According to the most recent medical hypotheses, inflammation and innate immune processes play a significant role in many psychiatric and neurological disorders. Alzheimer's disease (AD) is one of the most common cognitive decline disorders with a rapidly increasing incidence. The exact background of the development of the disease is still unclear, although in case of the inherited forms the role of mutations in presenilin-1 and -2 genes has been identified. The etiology of sporadic AD representing the largest burden to the society, however, is still an enigma [44, 45]. A new approach introduces AD as a disease that is caused by chronic inflammatory processes of the CNS [46, 47]. High-resolution, genome-wide association studies have recently shown a significant correlation between the polymorphisms of innate immune genes and the incidence of late onset of AD [48, 49]. Furthermore, several groups have reported that inflammatory mediators can be detected in brain regions affected by the disease and their plasma levels in patients show a significant increase, indicating that alterations in the function of the innate immune system plays an important role in the development of AD [50, 51]. In a mouse model of AD the inflammatory background of the disease was demonstrated by systemic poly-riboinosinic-polyribocytidilic acid (polyI:C) stimulation of the mother's TLR3 and RLR receptors in the pre-natal period. This treatment triggered inflammatory cytokine production in the embryonic brain associated with decreased neurogenesis and

cognitive development, and later caused a significantly enhanced appearance and deposition of Aβ aggregates in adult animals [52, 53]. Furthermore, re-stimulation of adult mice with polyI:C led to an AD-like phenotype [54]. Activation of the innate immune receptor NLR family, pyrin domain containing 3 (NLRP3) and subsequent activation of the NLRP3/Caspase-1 axis was also reported to play an important role in the pathogenesis of AD [55]. The inflammatory hypothesis is also supported by earlier clinical observations, which showed a positive correlation between the acute and chronic inflammatory state of the CNS and the acceleration of cognitive decline [56].

Other neuropsychological consequences of the activation of innate PRRs are also known, such as onset/worsening of bipolar disorder, major depression, anxiety, and schizophrenia symptoms. '*Sickness behavior*' is an important term not only in PNI but also in general psychiatry reflecting the effect of inflammatory cytokines on mood and behavior. This alteration in psychological state is characterized by lethargy, social isolation, and decreased physical activity [57, 58]. The common mediators of sickness behavior involve proinflammatory cytokines and IFNγ, which can affect the brain chemistry of mood regulators such as kynurenine, tryptophan, and monoamines [59]. In rodent models brain derived neurotrophic factor (BDNF) is claimed to have a pivotal role in depressive-like behavior and inflammatory cytokines, especially IL-1β was shown to inhibit the expression of BDNF [60]. In depression and anxiety-like behavior, the TLR3 and RLR-mediated effects also appeared to be BDNF and kynurenine pathway-dependent in mice [61, 62]. Several studies point to a causal relationship between inflammatory clinical conditions, certain cytokine-based therapies and depression [59]. Cancer and human immunodeficiency virus (HIV) patients, who receive type I IFN therapy, develop cognitive and neuro-vegetative symptoms of depression [63, 64]. Well-known comorbidities with depression have been documented in cases of rheumatoid arthritis, cardiovascular disease, or myocardial infarction where the patients exhibited elevated levels of inflammatory markers [65, 66]. It is also worthwhile to note that antidepressant therapies (tricyclics, selective serotonin reuptake inhibitors (SSRIs), electroconvulsive shock therapy have been reported to reduce inflammatory markers [59, 67]. The symptoms of depression caused by IFNα therapy is also responsive to treatment with SSRIs but antidepressants have only a minor restoring effect on the balance of HPA axis function [68]. Expression profiling of serum samples and monocytes from patients with major depression and bipolar disorder revealed common regulatory changes, increased levels of inflammatory markers including IL-1β, IL-6, TNF-α cytokines and C-reactive protein (CRP) [69]. Interestingly, in a small cohort clinical study Söderlund and colleagues found a substantial increase in IL-1β levels of cerebrospinal fluid of bipolar patients, but this elevation was higher in the subgroup of patients who experienced a recent manic episode [70]. Another group demonstrated that the concentration of the chemokine CCL2 and pentraxin 3 (PTX3) produced by monocyte-derived macrophages were significantly higher in the serum of patients with bipolar depression than in normal controls [71]. This indicates the importance of the affective state to modulate the inflammatory tone.

Recent research also suggests a link between innate immune processes and the etiology of schizophrenia, a psychotic disorder with extremely high prevalence. Recent studies demonstrated that antipsychotic-naïve patients with first-episode acute psychosis exhibit an inflammatory phenotype already at this early stage, and the initiation of treatment can resolve this anomaly as reviewed by Suvisaari and Mantere [72]. Prenatal infections and consequent TLR activation are also suggested to be important in the etiology of this disease [73-75]. A large cohort study also found an association between the genetic polymorphism of TLR2 and schizophrenia in the Korean population [76]. The importance of innate immune mechanisms was further supported by showing the involvement of the complement system in schizophrenia [77]. Being at the interface of immunology and biological psychiatry these results underscore the emerging theory of the immune background of schizophrenia. Although many aspects of the underlying mechanisms have not been elucidated yet, several cells and factors have already been identified as potential candidates involved in the pathology of the disease. One important mechanism relies on the TLR-mediated activation of the monocyte/macrophage system. A recent study found that the expression levels of TLR3 and TLR4 were significantly higher in monocytes of schizophrenia patients than in normal controls. Monocytes of these patients exhibited lower amounts of intracellular concentration of IL-1β after polyI:C (TLR3 ligand) or LPS (TLR4 ligand) stimulation [78]. The authors interpreted their results by supporting the inflammatory hypothesis, since the blunted monocyte/macrophage response and the inefficient clearance of pathogens could lead to low-grade inflammation in schizophrenia patients. Furthermore, the role of microglia considered as resident macrophages of the CNS were also suggested to be critical in the neuropathology of schizophrenia. Upon activation these cells produce various proinflammatory cytokines and free radicals thereby contributing directly to neuronal damage and degeneration. Typical and atypical antipsychotics can prevent the release of these cytokines by inhibiting microglia that raises the possibility of new treatment options [79, 80]. The reverse modulation of the innate immune response is also possible. Clinical studies showed that depression decreases the activity of innate, as well as adaptive immune processes [81]. Evidences suggest that stress can also lead to neuroinflammation *via* PRR activation. The TLR4-NF-κB pathway was shown to be activated in the prefrontal cortex of mice following exposure to stress. The results suggested the role of bacterial translocation in the TLR4-mediated inflammatory process in the CNS pointing out to the importance of increased intestinal permeability ('*leaky gut*') in stress or depression [82, 83]. Thus, the cross-talk of the CNS and the immune system in psychiatric and neurological disorders represents a multi-facet feed-back circuit that works rather as a single, integrated entity, than two or more synchronized systems. However, very recently this functional unity was completed with an additional element: the gut microbiota.

THE INTERFACE OF GUT, IMMUNE AND NERVOUS SYSTEMS AND THE MICROBIOTA

Multicellular eukaryotes live in mutualistic or commensal association with diverse communities of microorganisms. The highest number of microbes, which co-evolved with the human population, is localized to the lower intestinal tract and preferentially comprises anaerobic bacteria. The term "human microbiome" involves all constituents of the microbial community of a given individual including the collection of genes, proteins, metabolites and other microbe-derived molecules. Recent metagenomic studies also revealed that the composition of the gut microbiota is relatively stable but is shaped by genetic and environmental factors including maternal vertical transmission, infections, diet, stress and antibiotics. It is similar in family members but independent on nations or continents and based on the prevalence of certain strains of bacteria can be classified to enterotypes exhibiting different species compositions such as the dominance of *Bacteroides*, *Prevotella* or *Ruminococcus* [84], reviewed by [22].

Although the gut microbiome acts as an independent functional unit, it is tightly connected to and is in continuous contact with the mucosal immune system. It exerts important functions such as protection against pathogens, intake of dietary nutrients, and metabolism of toxic agents. It is also involved in remote functions such as pain perception in the skin [85] or fat deposition in the liver [86]. Thus the microbial cohabitates are essential components of human health and well being. However, the means how the human microbiome, which involves several hundreds of various microbial species that outnumber human somatic cells about ~10 and human genes about ~150 fold, impacts on various physiological functions is still poorly understood.

During embryogenesis the gut and the brain develop from a common tissue. Recent findings revealed that the gut-brain axis is not restricted to the regulation of the psychological status of the gastrointestinal (GI) tract but is extended to the mutualistic interactions of the gut microbiota with brain functions as well as to neurological and metabolic diseases. The bidirectional communication between the GI tract and the CNS is well established, but studies on the communication between the gut microbiome and the central nervous system have emerged only recently [87]. This mutual communication operates at the level of multiple modulatory signals originating from the human microbiota. It involves neural pathways such as the enteric nervous system (ENS), which is an essential component of the gut-brain axis as it controls motility, secretion, absorption, and blood flow. It receives signals from the intestinal epithelium, enteric endocrine and immune systems and through the sensory pathways signals to brain areas involved in emotion and cognition [88]. The hormonal pathways involve the regulation by enteroendocrine cells and bacterial neuropeptides, whereas the humoral pathway includes cytokines, neuropeptides, bacterial metabolites and hormones, which collaborate with signaling molecules to activate the mucosal immune system [22]. In contrast, the brain mediated factors targeting the microbiota act through stress, regulation of intestinal permeability and motility and the release of neurotransmitters and mucus (reviewed by [89]). Recent results also suggested that the gut microbiota modulates brain functions of the host through the gut-brain axis (reviewed by [90]) and has an impact on the behavioral phenotypes as well.

The first observations on the possible cross-communications between the microbiota and the central nervous system came from clinical observations showing that administration of oral antibiotics results in the improvement of patients with hepatic encephalopathy, a neuropsychiatric disorder [91] and inflammatory GI diseases often display correlation with depression or anxiety [92]. Animal experiments also revealed that certain pathogenic enteric bacteria such as *Citrobacter rodentium* provoke anxiety-like behavior in the early phase of infection, but the memory dysfunction of these mice could be prevented by daily treatment with probiotics [93]. The effects of microbial colonization on the development of brain plasticity was also tested by the reaction of HPA to stress and was compared in germ free (GF), specific pathogen free (SPF) and gnotobiotic mice. The authors observed elevated plasma propiomelanocortin (POMC/ACTH) and corticosterone levels in response to restraint stress that was associated with reduced levels of BDNF in the cortex and hippocampus as compared to SPF mice. The HPA stress response however, could be reversed by *Bifidobacterium infantis* and showed that microbes at an early developmental stage are required for developing a competent HPA system [94]. The attenuation of pro-inflammatory immune responses in line with increased levels of the serotonergic precursor tryptophan could be induced by the treatment of rats with bifidobacteria suggesting the anti-depressant potential of that probiotic strain [95]. Furthermore, experiments performed with germ-free mice indicated that the expression of genes implicated in anxiety and stress reactivity was associated with decreased mRNA expression of the N-methyl-D-aspartate receptor (NR2B) subunit in the central amygdala, with elevated levels of BDNF and with decreased serotonin receptor 1A (5HT1A) expression in the dentate granule layer of the hippocampus indicating the impact of the gut microbiota on behavior and neurochemical parameters of the brain [90].

Further studies focused on the role of various probiotics in modulating stress and anxiety behavior. Modification of the microbiota by certain probiotic formulations such as the combination of *Lactobacillus helveticus R0052* and *Bifidobacterium longum R0175* (PF) was shown to decrease stress-induced GI discomfort and exert anxiolytic-like activity by decreasing serum cortisol levels in healthy human volunteers [96]. Long lasting treatment of mice with *Lactobacillus rhamnosus* induced altered emotional behavior and the expression of the neurotransmitter γ-Aminobutyric acid (GABA) in the CNS in a brain region-dependent manner. As these alterations could not be observed in vagotomized mice this finding suggested that the vagus nerve may be involved in the communication pathway between the gut and the brain [97]. A mouse model of chemical colitis was shown to be associated with anxiety-like behavior that could be normalized by *Bifidobacterium longum NCC3001*, required vagal integrity but did not not involve gut immuno-modulation or the production of BDNF by neuronal cells. As *B. longum* can decrease excitability of enteric neurons, it may signal to the central nervous system through the enteric nervous system [98, 99].

Comparison of the behavior of GF and SPF mice exhibited significnt differenes as GF mice showed increased motor activity and reduced anxiety-like behavior, altered expression of synaptic plasticity-related genes, elevated noradrenaline (NA), dopamine (DA), and 5-hydroxytryptamine (5-HT) turnover in the striatum as compared to mice housed under SPF conditions [100]. These results indicate that the gut microbiota takes part in modulating both behavior and brain chemistry however, the linked regulation of all these changes remained to be uncovered.

Examples of inverse communication *i.e.* from the brain to the gut also exist and is based on the hypothesis that descending signals from the CNS can alter the composition and function of the gut microbiota in both rodents and primates. Control mice were characterized by high load of epithelial lactobacilli, while the level of bacteria was decreased in stressed mice showing that environmental and dietary stress can markedly alter the GI microbiota in mice [101]. It was also shown that 3 days after maternal separation a significant decrease in the level of fecal lactobacilli could be detected that correlated with the display of stress-indicative behavior and susceptibility to opportunistic bacterial infections [102].

A modulatory effect originating from the brain and acting on the gut microbiota can also occur. Stress-induced dysbiosis has been shown to results in increased levels of IL-6 and monocyte chemoattractant protein 1 (MCP1/CCL2) in the circulation. The mechanism behind this effect might include stress-induced changes in intestinal motility and mucin secretion. Stress also can increase noradrenaline concentration in the gut lumen and catecholamines including noradrenalin were shown to alter gene expression profiles in some bacteria and could boost the growth of certain microbial communities. Commensal microbiota has also been shown to cooperate with the myelin autoantigen to trigger autoimmune-mediated demyelination [103].

Microbial products have access to various tissues through blood circulation. Changes in microbiota composition induced by regular diet, antibiotics or probiotics can disturb the balance of the host's mucosal immune system and the composition of the gut microbiota resulting in altered cytokine profiles mediated by ligation of PRRs. For example *B. longum subsp. infantis str. 35624* has been shown to induce increased secretion of IL-6 cytokine by circulating peripheral immune cells and was shown to improve depression-like behavior in mice provoked by maternal separation [104]. A human study performed on age matched neonates also showed differences in the electrical activity of the brain measured by spatio-temporal analysis to EEG recordings. The authors concluded retarded transition of Cesarian section neonates, born under sterile condition, in early adaptation [105].

The significance of a healthy gut microbiota in humans has also been demonstrated by the high incidence of behavioral changes and psychiatric problems in patients with irritable bowel disease (IBS) characterized by unstable microbial communities of low diversity. This association was also revealed in patients with inflammatory bowel diseases (Crohn's disease and ulcerative colitis) linked to dysbiosis [106]. As a further proof of microbe-mediated effects exerted on the central nervous system was demonstrated by the beneficial effects of defined probiotic combinations on brain functions. To this end several observations indicated that various metabolic products of the intestinal microbiota can modulate brain functions and behavior of the host. Bacterial metabolites such as lactic and propionic acid have been shown to influence human behavior demonstrated by the association of high fecal concentration of propionic acid with anxiety in patients with IBS [107]. Carbohydrate malabsorption was associated with increased substrate availability for bacterial fermentation and was found to be linked to depression in females [108]. The tryptophan metabolite kynurenic acid exhibits antagonistic effects on excitatory amino acid receptors and is implicated in causing major psychiatric illnesses such as schizophrenia [109]. The neurotransmitter GABA has also been shown as a product of commensal lactobacilli and bifidobacteria in humans and other neurochemicals including noradrenaline, 5-HT, dopamine, acetylcholine could also be isolated from gut bacteria emerging as a novel tool for the treatment of neuropsychiatric diseases [110]. By using behavioral tests it has also been demonstrated that the composition of the microbiota has an impact on early brain development. Young mice housed in germ free (GF) conditions exhibited more exploratory and risk-taking behavior than mice bred at SPF conditions [90].

We propose the BIG-T theory ('Brain-Immune-Gut Triangle') in which the elements of the BIG-T comprising the brain, the immune system, and the gut microbiota have their well defined profile of functions (Fig. **1**). The main function of the immune system is to provide the two other subunits with protection. The gut microbiota on the other hand supports nutrition, while the brain's main functions are cognition and organization of behavior. Fine-tuning is continuously carried out by each element through feed-back mechanisms, which involve the effects of diet on immune functions and immune regulation affecting the behavior of intestinal microorganisms. The bi-directional communication of the microbiota and the brain *via* the gut-brain axis together with the functional and regulatory interactions of the immune system and the CNS is organized to a functional network where the brain, the immune system and the gut microbiota represent informational "hubs" of the system (Fig. **1**). Since bidirectional regulation is possible and presumably does exist *in vivo* at all levels of the elements of the BIG-T, complete understanding of the operation of this complex communication system will allow us to design novel therapeutic strategies in many gut/immune/CNS-related disorders.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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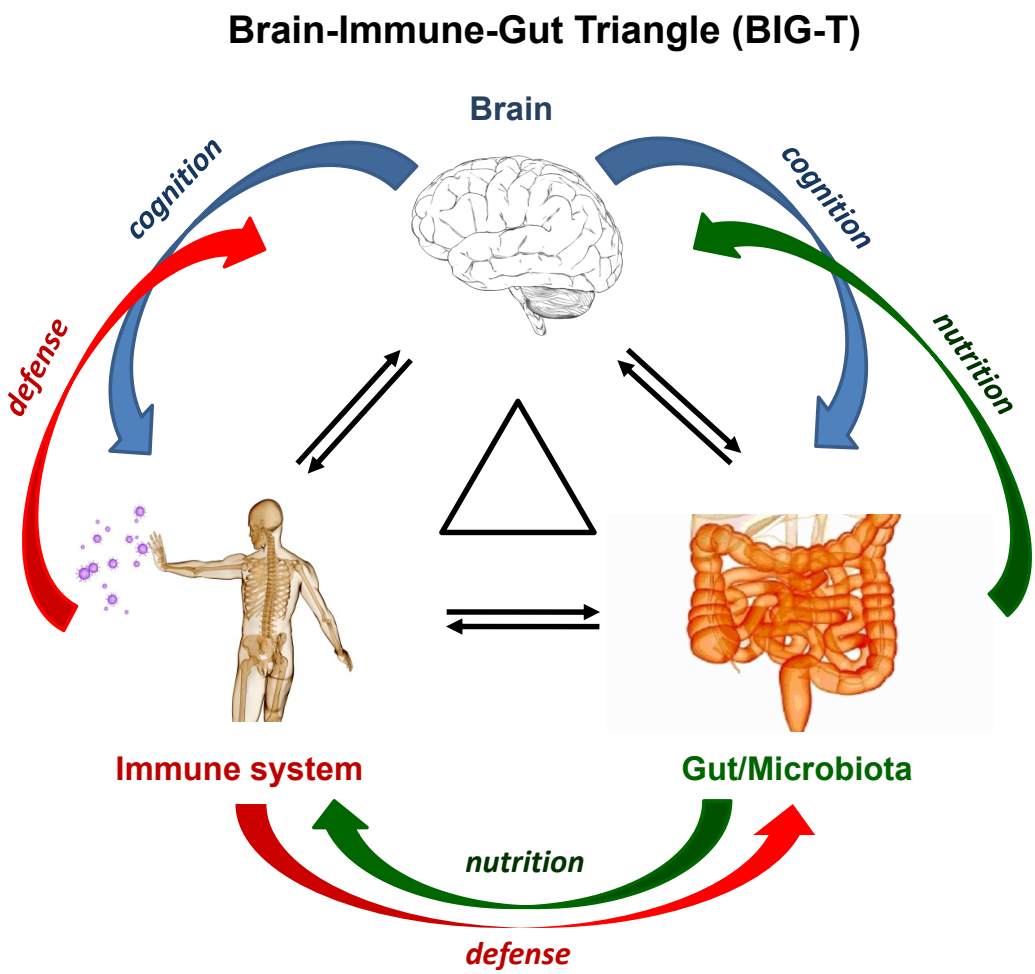

Fig. (1). The brain-immune-gut triangle as an integrated functional and regulatory entity. The BIG-T represents the brain-immune-gut systems as a single functional unit. According to this approach, immune processes, behavior, and diet/nutrition are tightly interrelated and inter-regulated. The brain, immune system, and gut microbiota represent informational hubs in this network. Bidirectional black arrows show feed-back fine tuning, while colored arrows designate functional activites of the individual systems.

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