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The Brain-Body-Microbial Communities: A Crosstalk and Stress Exchange Beyond the "Gut hypothesis"

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Abstract

For many decades, the consequences of "stress" have been perceived as a "unidirectional" pathway where some stressful life conditions cause "mental stress" that activates the brain's stress response systems, which sequentially affect many of the major body systems especially gastrointestinal tract. The striking upsurge in incidence of neuropsychiatric and neurodevelopmental disorders, in the last five decades, appeals to a crucial "bidirectional" interaction between the nervous system with other body systems. Such fast expansion of these disorders enforces also a causal role for environmental insults inflicted by the changing ecosystems as well as the modernization of human life style including lavish use of antibiotics, high hygiene standards and predominant utilization of urban western diet. It is also becoming clear that several neurological and psychiatric disorders are more and more being linked to a wide range of systemic dysfunctions including, most notably, immunological impairments and microbial manipulation. We believe that nervous system development and function are not only highly coupled with other physiological body systems but also with non-physiologic microenvironments created by pathogenic agents or dormant commensals. Direct or bystander effects of certain infectious agents or complex microbiome communities on brain development and function could modulate and evoke deviated behavioral responses and abnormal psychological outcomes. We think a better understanding of the basic components of this bidirectional interaction and the comprehensive characterization of the involved pathways will produce significant insights into the way nervous system diseases evolve and yield a novel array of therapeutic strategies. Here, we discuss different aspects of the dynamic crosstalk between the nervous system and microenvironments created by long-lasting pathogenic infections or by permanent commensal microbial communities. To pursue this goal, we review hypotheses and evidences that link certain pathogens or microbiome compositions to the development of neuropsychiatric diseases and/or neurodevelopmental disorders in genetically predisposed persons.

Keywords: Microbiome; Infections; Brain; Stress; Psychiatric; Neurodevelopmental

Introduction

The gut microbiotas have a critical impact on the health of the host. They guard against infectious agents, orchestrate body metabolomics, and control the absorption of drugs and the distribution of dietary fats [1]. However, microbiota has its own selective effect that extends beyond the gut. The microbiome actively participates in the development and performance of the central nervous system (CNS) [2]. A bulk of research has proven that while the gut microbiota have an impact on the CNS function, the brain can also alter the microbiome structure. Signaling molecules released into the gut lumen from lamina propria in response to psychological stress, under CNS control, can result in altered gastrointestinal motility, secretion pattern and intestinal permeability, changing the gastrointestinal environment and consequently microbiome composition [3]. Early life perturbations of gut microbiome can influence neurodevelopment and potentially lead to unfavorable morbid effects during adulthood [4]. These findings and many similar reports demonstrate bidirectional communication between the body and CNS reflecting an emerging view that there is a stress exchange between the brain and the body that might be mediated through microbiome alterations and/or overt infections with high or low virulent pathogens.

Stress is a ubiquitous state that has a variable effect on all individuals. Stress can be mental or physical. Mental stress comprises challenge, threat or worry about upcoming undesirable events. Such stress initiates the stress response systems of the brain, which in turn adversely influence the major systems of the body particularly gastrointestinal functions [5].

The notion that an infectious agent may be implicated in the pathogenesis of mental illness is hanging around, in the field of medical research, for long time. An editorial in the journal of "Scientific American", 1896 proposed that some mental disorders could be consequences of infection [6]. Yet, in recent years, an exceptional consideration of pathogenic organisms away from their typical role in infectious diseases has emerged. Long-standing clinical findings and recent epidemiological and scientific reports suggest that many nervous system diseases that thought to be strictly nervous in origin, exhibit heterogeneous phenotypes, which are expressed as symptoms in other physiological systems and/or at brain–systemic interfaces [7]. One of the most noticeable features of many neuropsychiatric (e.g. affective) disorders is their variance, with individual differences concerning susceptibility to disease, the combination of disrupted systems, and in the therapeutic and/or adverse responses to medication [8]. Microorganisms generate several compounds that can modulate brain functions [9]. Autoantibodies have been identified in Schizophrenic [10], bipolar and other affective disorders [11] and Alzheimer's disease [12]. High levels of inflammatory markers and cytokines [13-

15] have been detected in those patients, proposing an autoimmune inflammation as an underlying mechanism of such diseases. Yet non-confirmed, a pathophysiology of how specific microbial agents orchestrate the inflammatory process started to evolve in the recent few years.

Although the principal mechanisms are ambiguous, it is rational to suggest that postnatal development, mainly CNS functions, are affected by the same variables that influence the structure and function of human microbiome. The intrapersonal variation of microbiome composition is not parallel and considerably less than interpersonal variation reflects the individual best control measures to deal with dietary, pharmacologic or other disturbances on microbiome structure and function [8]. Several studies link diet to different forms of psychiatric diseases, such as schizophrenia, mono- and bipolar depression [16], as well as attention deficit–hyperactivity disorder (ADHD) [17], and autism [18]. It is also a fact that diet has a crucial share in influencing the microbiome structure and function. A number of psychiatric and neurodegenerative disorders with altered behavior, like autism and schizophrenia, demonstrate also digestive troubles, and diet-related manifestations. It has been proposed that autistic children have a microbiome composition different from non-autistic ones [19]. Even with no established relationship, yet a number of researchers think that microbiome investigation may lead to early diagnosis and subsequently early treatment of autism even before the onset of symptoms [9].

Impact on Host Behavior: An Action of a Single Pathogen or an Entire Microbial Community

Single-pathogen model

While it is difficult to differentiate, it is has reported that pathogens could induce behavioral changes in the host by direct and/or indirect actions. The immune–neural interactions, induced by some pathogens, make it hard to conclude the mechanism of host's behavior alteration, whether a direct impact from the pathogen or an indirect result of the evoked immune responses. Moreover, some pathogens secrete immunoactive neuropeptides similar to those generated by immune reactions [20]. The secreted compounds could modulate immune [21] as well as nervous functions. They can be detected in the serum and CNS but with no clue to their source [22].

Most of the working hypotheses for neurodevelopmental and psychiatric disorders, especially schizophrenia, assume that most cases are the result of infections and/or other environmental insults that activates a dormant genetic background in genetically predisposed individuals. These distinct gene-environmental interactions took place a long or short time before the onset of the clinical disease. The "single pathogen" suggestion means that infection with a certain infectious agent is considered an environmental insult that activates a genetic background and lead to a cascade of complex interactions that ultimately ends up with the development of a psychiatric disorder. However, this does not mean that a specific single pathogen is responsible of all psychiatric disorders. It seems that a range of infectious agents utilize common mechanisms to induce some neuropsychiatric disorders [23]. Therefore, any pathogen (viruses, bacteria or parasites) that can activate a predisposed genetic elements and can drive the same cascade of interacting pathways, is a candidate pathogen that might precipitate a psychiatric disorder.

However, the infection hypothesis of psychiatric disorders was not an easy testable theory. A series of theoretical challenges and practical problems, have hampered the investigation of such theory.

Some of these limitations include, the scarce information about disease pathogenesis, limited and atypical animal models [24,25] as well as the lack of diagnostic or prognostic laboratory biomarkers [26] that could serve as indicators of the investigative process. Failure of this hypothesis to fulfill many of the "Koch's Postulates" [27] about microbial agents and huuman disease was another major obstacle. The theory does not follow the Koch's assumptions that specific infectious agents because clearly delineated disease states which cannot exist without the causative agent that is able to induce a similar disease in animal models. Most psychiatric disorders are believed to be multi-factorial with shared pathways in the complex response to infection. Moreover, many of the susceptibility genes are diverse determinants of the outcome of infection. In addition, individual variance is a common finding in those diseases and animal models of such complex diseases are very limited.

Schizophrenia and infection hypothesis: Schizophrenia is the most studied disease concerning its relation to infections. An accumulating epidemiologic and clinical data have offered proof that in-utero infection is involved in schizophrenia pathophysiology [28]. Though no genes specifically related to susceptibility for schizophrenia have been discovered to date, genetic and neuropsychological studies suggest that to get the disease, possible suspected schizophrenia gene, should be expressed [29,30]. The fact that there is a number of schizophrenia subtypes, as well as great variability in the age of onset and course of the disease, suggests multifactorial etiology [31]. Theories include genetic, developmental, viral, immunological, biochemical, nutritional, and stress causes [32]. However, these proposed theories only explain the disease on a mutual basis. For instance, biochemical theories of schizophrenia usually suggest a genetic predisposition. Also, the most favored neurodevelopmental hypothesis, include genetic and epigenetic elements, as well as obstetric factors, early-life environmental insults and in utero stress exposure [33,34].

Many cases of schizophrenia have a positive association with past infection with almost eighteen microorganisms mostly viruses [6]. Prenatal influenza [35], perinatal Rubella [36], neonatal Enterovirus [37] and maternal Herpesvirus [38] have been incriminated in the pathogenesis of schizophrenia. *Toxoplasma gondii* [39], Human immunodeficiency virus (HIV) [40] and Herpes Simplex (HSV) [41] have been also reported as possible factors. Apart from the underlying mechanisms, that are not well understood, certain statistical and epidemiological conclusions can be drawn. Recent onset schizophrenia is associated with increased transcription of Human endogenous retrovirus type W (HERV-W) and increased levels of antibodies to Cytomegalovirus (CMV). Past infection with HSV-1 is linked to cognitive impairment in patients with stable schizophrenia. Maternal exposure to infectious agents is associated with a rise in schizophrenia risk rate among the offspring [39].

The *Toxoplasma*/schizophrenia inter-relation was intensively investigated and it represents the most understood model so far for a neuropsychiatric disorder. Therefore, a more comprehensive elucidation of this model will better demonstrate the mechanisms underlying the development of neuropsychiatric illnesses.

***Toxoplasma*, brain and schizophrenia: An infection connection:** Among many pathogens linked to psychiatric disorders [42,43], most of the attention is centered on *Toxoplasma gondii*, a neurotropic parasite that has a life-long latent phase after a usually short and asymptomatic acute stage in immunocompetent individuals [44]. The parasite is never cleared from the nervous system where cell-mediated immune response mediates its long-life existence [45]. This obligatory

intracellular parasite affects one-third of the world's population [46], and produces a wide range of clinical syndromes with an exceptional severity in immunocompromised patients [47]. Early trans-placental infection might result in a fetal multi-system affection that includes serious CNS abnormalities [39].

For many decades, latent *Toxoplasma* infection has been regarded as completely asymptomatic in immunocompetent individuals. In view of recent findings suggesting a parasite's survival power making it in adequate control of host's machinery, questions have been raised on the "apparently" peaceful parasitic existence in the host. The theory that *Toxoplasma* infection could drive the development of some neuropsychiatric illnesses, especially schizophrenia, was created many years ago. Different studies have demonstrated that *Toxoplasma* alters the behavior of its rodent intermediate hosts (mice and rats) boosting their chance of being predated by cats [48,49]. It has been also reported that latent toxoplasmosis patients are 2.65 times more susceptible to be engaged in car accidents than non-infected individuals [50]. Suicide attempters had also been shown to have significantly higher values of anti-*Toxoplasma* IgG antibodis [51].

Toxoplasma gondii tends to reside in brain neurons, especially glial cells, which are profoundly involved in forming the scaffold for brain structure, guiding the growth of other brain cells. The cell culturing studies confirmed the affinity of *T. gondii* to glial cells, especially astrocytes, [52,53]. *Toxoplasma* infection can also lead to an infiltration of CNS with a significant trail of immune cells (CD4+ and CD8+ cells) [54]. These cells bind to adhesion molecules and encounter parasitic antigens presented by glial cells. This process activates secretion of INF-γ which in turn induces microglia to demonstrate phagocytic activity and produce INF-γ and TNF-α. Both cytokines are believed to express enough action to limit parasite replication and stimulate cytotoxic T-cells to destroy parasitized cells [55]. Microglia changes has been reported to be a mainstay for the development of many behavioral and psychiatric disorders [56]. On the other hand, glia is believed to be centrally involved in schizophrenia. Studies on postmortem brain specimens of schizophrenic patients have also revealed several glial deformities [57], including low numbers of astrocytes [58].

The *Toxoplasma* ability to infect the brain and reside there forever producing a low grade encephalitis and inducing some structural changes and cognitive impairment [59] is consistent with many aspects of schizophrenia pathogenesis [60]. While there is no specific assumption can be drawn, it is notable that several studies [61-63] propose a potential link between schizophrenia and *Toxoplasma* infection. This proposal has been boosted by studies demonstrating an in vitro anti-*Toxoplasma* activity for some medications used in schizophrenia [64,65]. Anti-*Toxoplasma* chemotherapeutics as well as dopamine antagonists were reported to regain the normal behavior of experimental murine models, signifying a neuro-chemical mechanism underlying *T. gondii* alteration of host behavior [66].

Schizophrenia-*Toxoplasma* coevolution: Potential costs of tolerance: Human history cannot be understood well without understanding the causes and consequences of human disease [67]. This suggestion has become fully evident over the past few years as the outcomes of infectious diseases have been revised in an untraditional context. For most of the 20th century, the prevailing view was that disease-causing infectious agents ultimately should progress toward benign coexistence with their hosts. According to this view, severe acute diseases were seen as a transient condition of maladaptation [68]. This belief assumed also that the host has retained a permanent state of "tolerance" and is able to indefinitely limit the damage caused by a given pathogen burden. Long-term adaptation and peaceful host-pathogen coexistence postulation has made any future drastic consequence of infection practically impossible. According to the same view, latent *Toxoplasma gondii* infection, with its life-long brain existence, has been considered as a benign co-existance of the parasite and described as a "symptomless" state of the disease. However, it is widely accepted in health sciences that pathogen burden and host's well-being are not always well correlated [69], but that rather logic decoupling for the sake of better understanding of host-pathogen coevolution have been mostly overlooked. Coevolution is exceptionally critical in host–microbe paradigm due to the intimate association and the robust selective pressures exerted by each one on the other [70]. The reciprocal traits possibly engaged in host-pathogen coevolution include pathogen infective ability and host resistance; pathogen's ability of host selection and host's pathogen-avoidance behaviors; as well as the host ability to eradicate the pathogen versus the ability of the pathogen to evade host defenses and establish infection [71]. Consequences of coevolution are hard to demonstrate because the genetics of host–pathogen communication does not usually follow the straightforward gene-for-gene pattern. For example, human resistance and/or tolerance to parasites is frequently polygenic with a range of genetic mechanisms ensuring effective host resistance [72]. A further complication is phenotypic plasticity [73] which is best demonstrated by the adaptive immune response, which lets a single specific genetic machinery to defend against a enormous number of different pathogenic species and/or strains [71].

One postulated mechanism for how *Toxoplasma* infection could affect personality in humans is the local brain immune microenvironment that is involved in maintaining *T. gondii* quiescent. In its pursue to "tolerate" *Toxoplasma* infection, the human body unleashes immune responses that alter cytokine levels, which consequently influence the level of neuromodulators [74] such as increasing dopamine [75]. *Toxoplasma gondii* provides a good model of the manipulative power of the parasite exerted on its host. To accomplish its own selective advantage, the parasite can modulate host behavior. Sexual reproduction of *T. gondii* takes place only in the definitive host (felines), therefore, strong selective pressures enforce the parasite to evolve mechanisms to accelerate its transmission from the intermediate host (mice, rats etc.) to the definitive cat host to complete its life cycle. Thus *Toxoplasma* deliberately induces behavior changes in its intermediate host so as to promote its urge to move to the definitive host. Some studies have demonstrated that *T. gondii* causes an increased activity and a suppressed innate fear and predator vigilance behavioral traits of mice [76], each might help *Toxoplasma* exit from the intermediate murine host. Moreover, *T. gondii* appears to alter the rats' cognitive perception of cat predation risk, turning their innate aversion into a 'suicidal' fatal feline attraction [77-79].

Toxoplasma and schizophrenia pathophysiology: Hypotheses, mechanisms and pathways: Schizophrenia is a multifactorial disorder, where multiple etiologic factors interact to precipitate the disease through a heterogeneous array of pathways. Any correlation between *Toxoplasma* infection and the pathophysiology of schizophrenia is expected to happen only in a small percentage of infected individuals, and is valid to only a number of schizophrenic cases, however, there is more than a subtle evidence that link them together [80,81].

Many hypotheses have been proposed to establish a reasonable explanation to a possible role of toxoplasmosis, especially its latent phase, in the development of schizophrenia. An account on the meurodevelopmental theory was presented in the previous section (Schizophrenia-*Toxoplasma* coevolution).

A cytokine hypothesis was also suggested [82,83]. It states that early maternal immune activation most probably due to infections, results in premature in utero exposure to high levels of cytokines which gradually leads to the development of schizophrenia usually during adolescence [84]. In addition to their immune function, cytokines are crucially involved in the process of neurodevelopment. Cytokine ligands are expressed on several cells of the fetal brain. They are involved in many processes that pursue a tightly regulated pattern of neurodevelopment that is crucial for efficient adulthood pattern of neural functioning [82]. Many epidemiological and laboratory findings support this hypothesis. Abnormal patterns of expression of some cytokines have been demonstrated in both the brain and peripheral blood of schizophrenic patients [83]. Epidemiologic reports relating schizophrenia to early-life infections started to emerge more than 50 years ago. Some children born to mothers infected with influenza, during the pandemic of 1957, developed schizophrenia later in life [85]. *Toxoplasma gondii* infection fits better in the cytokine hypothesis of schizophrenia. Due to an early-life activation of the immune system by in-utero *Toxoplasma* infection and/or persistence of latent infection, which is not radically cleared by the immune system. As a result, an imbalance between the T-helper type-1 (Th-1) and Th-2 immune responses prevails. Interferon (IFN)-γ is the main cytokine involved with acute as well as with chronic resistance to *T. gondii* infection [86]. Some reports have suggested a relationship between schizophrenia and IFN-γ, a major immune-activator in the CNS [87]. During prenatal exposure to *Toxoplasma* infection, a considerable rise of placental TNF-α levels takes place [88]. Elevated levels of TNF-α are evident in the serum of schizophrenia patients [89]. This disturbed immune pattern could be associated with indoleamine 2,3 dioxygenase (IDO) inhibition that ultimately leads to tryptophan depletion and accumulation of kynurenic acid in specific parts of CNS. It is believed that this specific pattern of disturbed metabolomics might lead to the emergence of schizophrenia [90].

Here, we tackle one of the most accepted theories, that explains Schizophrenia-*Toxoplasma* interaction and intersect with other hypotheses, which is the "neurotransmitters theory".

Neurotransmitters theory: Different types of neurotransmitter irregularities have been implicated in the pathogenesis of schizophrenia. Most of the studies investigating a possible neurotransmitter basis of schizophrenia have been concentrated on monoamine compounds especially dopamine and serotonin, amino acid transmitters mostly glutamate and neuropeptides [91-93]. Excessive dopamine or deficient glutamate function appear to be the most reasonable pathways. However, disturbances of other neurotransmitters such as noradrenalin and γ-aminobutyric acid (GABA), may also have a role [94]. The serotoninergic (5-HT) system has also been frequently implicated in schizophrenia [95].

Dopamine is considered the main neurotransmitter engaged in the pathophysiology of schizophrenia [96]. However, some studies viewed glutamate as a better candidate to explain the heterogeneous symptoms of schizophrenia [97]. Glutamatergic neurotransmission has been linked to a number of physiological and with specific pathophysiological processes, including schizophrenia [98]. Glutamate has been reported to present in nearly all areas of the brain, in contrast to dopamine which is confined to only certain parts [97]. A diminished release of glutamate has been detected in the frontal and temporal cortices of schizophrenic patients [99].

The "dopamine hypothesis" proposes that schizophrenia-associated symptoms are linked to excess dopamine release in specific brain regions [97]. Dopamine release can disrupt the fornix section of brain leading to the development of psychosis [61]. Dopamine overproduction and activity is proposed to be engaged in schizophrenia pathogenesis since drugs that decrease brain's dopamine levels are likely to mitigate the positive symptoms of schizophrenia. On the other hand, amphetamines that increase dopamine levels, has been reported to accentuate schizophrenia symptoms [100]. Dopamine hyperactivity seems to be linked to the positive symptoms of schizophrenia [101]. Parasitosis might contribute to the increase of the dopamine level in mice brain [102,103]. Similarly, studies on experimental animal models of toxoplasmosis have showed that the parasite modulates dopamine, norepinephrine, and other neurotransmitters, in a pattern similar to that encountered in schizophrenia patients [39]. The host's defense mechanisms against *Toxoplasma* infection might ultimately lead to a decrease in serotonin and an accumulation of dopamine. While the host is trying to control latent toxoplasmosis through a T-lymphocyte-driven mechanisms [104], these activated T-helper cells secrete IFN-γ which in turn induces IDO enzyme [105]. Through the kynurenine-pathway, IDO leads to tryptophan depletion resulting in the accumulation of tryptophan-degradation products [106] that may result in excess dopaminergic tone. Moreover, a single study has been demonstrated that *T. gondii* by its own is able to synthesize dopamine [107]. Some studies showed that dopamine is one of the key compounds related to psychosis (e.g. schizophrenia, and bipolar disorder) in latent toxoplasmosis patients [108,109]. Another report proposes that endocannabinoids-induced by *T. gondii* infection may also be associated with abnormal behavior [110].

Therefore, the interaction between latent *Toxoplasma* infection, and the host immune system that lead to neurotransmitters irregularities, could represent a reasonable model for the evolution of, not only schizophrenia, but other related personality disorders [111].

Entire microbial community (microbiome)-model

Bidirectional modulation: There is now an accumulating literature that defend the idea that gut microbiome plays a role in early programming as well as later responses of the stress system. Recent breakthroughs have been made in the neurobiological knowledge of the host response to acute and chronic stress. This has evolved a better insight of the complex brain-gut interactions and their modulation in health and disease [112]. The old, one-way stress model indicates that certain stressful life events have been triggered the onset or exacerbate of several common chronic functional and organic disorders especially of the digestive system. These gastrointestinal diseases include inflammatory bowel disease, reflux oesophagitis, and peptic ulcer [5].

Gut microbiome and the brain: bidirectional communication with an "immune bridge": The assumption that the gut microbiota may contribute to the risk and pathogenesis of many psychiatric and neurodevelopmental disorders, is a testable hypothesis. Genetic and environmental factors individually or combined are not enough to explain the rising incidence of several psychiatric and neurodegenerative illnesses. A missing link might activate a dormant genetic predisposition and arrange the non-specific environmental factors into a targeted and compact sequence of events. This activated cascade could ultimately lead to behavioral changes that characterized those diseases. Consequently, a new paradigm has emerged that takes into account the individual genetic traits, the impact of environmental factors, the individual infectious experience and/or microbiome structure together with an immunologic basis that mediate the interaction of all these variables to develop neuropsychiatric disorders. It is now comprehensible that the balance between the host and his microbiome composition, in both healthy and morbid states, depends

profoundly on a very well-tuned balance of immune tolerance and response. The massive interaction between the immune system and the diverse microbial communities is evident in three major observations. Firstly, the presence of noticeable innate and adaptive immune responses to the microbiome constituents in health and disease. Secondly, alterations, in microbiome structure and/or function, took place in patients with genetic immune deficiencies suggesting an immune control on microbiome. Thirdly, deviant immune system responses to non-relevant antigens, including self-antigens, imply a microbiome-derived immune modulation [113].

Co-evolvement of microbiome assembly and nervous system functions: Shaping of the microbiota take places a parallel course to neurodevelopment and they both have similar crucial developmental opportunities sensitive to adverse actions. The 10-100 trillion symbiotic microbial cells harbored by each person (i.e., the microbiome) [114] are involved in the evolution and function of the immune system. This system consequently works to balance clearance of pathogenic microbes with tolerance of beneficial commensal ones. Recent studies [115,116] back the suggestion that the changes in host microbiome modulate its immune response evoking a "remote control" effect on distant organs that may lead to diseases. The microbial population residing in the small and large intestine represents the largest microbial population of the human microbiota. Therefore, dysbiosis of the gut microbiota could not only be related to several intestinal but also extraintestinal diseases. Brain is one of these distant organs that seems to be the most affected by gut microbiome dysbiosis [117]. Dysbiosis of gut microbial structure and function has been linked to many behavioural and neurophysical morbid changes. Most, chief neurological and psychiatric disorders display immunological abnormalities such as high levels of inflammation and deviant innate and adaptive immune responses [7].

The assembly of the microbial community during infancy remains poorly understood despite being essential to human health [118,119]. This construction of the microbiota can lead to either negative or positive effects on health. Metagenomic investigations of the microbiome of human gut suggested a crucial part of early postnatal environmental exposures in shaping the phylogenetic organization of the future gut microbiome in adulthood. However, the human intestinal microbiota changes from being sparsely populated and variable to an organized assembly towards an adult microbiome structure takes place during the first three years of life [120]. The facultative anaerobes such as Streptococcus, Enterobacteriaceae and Staphylococcus are the first gut colonizers consuming oxygen, and therefore creating an anaerobic environment leading to predominance of strict anaerobes such as Clostridium, Bacteroides and Bifidobacteria [121]. Characteristics of the gut microbata consotorium and its gene content are allocated to family members and passed on to next generations [122]. Nutrition in this early post-natal phase of life is considered one of the crucial environmental exposure events that determine microbiome structure. A recent study revealed a feeding mode-dependent difference in terms of diversity of the microbiota, the interactions among them as well as their interplay with host genes. During the first two years of post-natal period, breastfeeding is crucial for establishing gut microbiome composition [121] and the development of a healthy host-microbiome consortium in human infants that could continue for the entire healthy adulthood [123]. Apart from antibodies that partly protect newborns from infection, breast milk contains immunoactive substances, such as cytokines (especially IL-10), growth factors and antimicrobial enzymes such as lysozyme. This sequence of events could suggest temporal axis of co-evolution of the immunological and nutrient characters of breast milk and the early life formation and maturation of the gut microbiome and of the innate and adaptive immune responses [124]. A large-scale cohort study supports this suggestion and indicates that breastfeeding may have a positive effect on children's and adolescent's mental health [125].

Microbiome-driven immune responses regulate nervous functions: Gathering evidence proposes that the immune responsiveness of any host is mostly molded by his own microbiome, with inferences for immunity to infection, magnitude of immune pathology and autoimmunity. The microbiome has been linked to the initiation of a deviant immune response and also been shown to modulate brain development and behavior in animal model systems. The gut microbiome has a critical role in the development of the immune system. The body microbiota, like invading pathogens, exhibit the ability to activate both innate and adaptive immune responses. The stimulated innate immunity, early in life, leads to the maturation of the gut-associated lymphoid tissue (GALT), and acquired immunity, through activation of both local and systemic responses. Innate immune responses to the microbiome constituents, together with physical barriers, may avert Th-cell-driven actions towards microbiota antigens [126]. As the innate responses are short of specificity and lack memory, it is frequently hard to recognize whether innate responses to microbiota-pathogen shared molecular patterns have been activated by the microbiota or pathogens. Moreover, gut microbiota exercises its protective power, against pathogens, through accelerating the metabolism of nutrients required for pathogen's survival, as well as the production of growth-inhibitory molecules [127]. However, the exact role of Th cells in microbiota control is not yet fully understood [126].

After stabilization of the gut microbiota community, the constant stimulation of the immune system by several structural components of the microbial cells leads to production of a wide range of lymphocytes and cytokines. In a state of homeostasis, the gut microbiota induces a chronic state of low-level activation of the (innate) immune system in the host, in which bacterial particles stimulate intestinal macrophages and T cells to produce pro-inflammatory cytokines; interleukin (IL)-1β, tumor necrosis factor-α, IL-18 [128]. This status of "low-grade physiological inflammation", is a prompt and efficient machinery combating pathogens [129]. The produced cytokines create a basal state of immune activation that starts at the intestinal mucosal surface and eventually affects the entire body especially the nervous system. The low level exposure of immune cells to the bacterial cell wall components such as lipopolysaccharides (LPS), is essential in the establishment and maintenance of mucosal homeostasis [130].

However, the power of gut microbiota exerted through stimulation or suppression of the immune system, might extend beyond the control of the pathogens themselves. Microbiota modulation of the functions of myeloid cell, will unavoidably extend to T cell responses. All these cascades and others are involved in the creation of immunologic and biochemical microenvironment that gradually modulate nervous functions. The brain is the commonly targeted and the most vulnerable organ to the microbiome-drive state of continuous immune stimulation and a constant low-grade inflammation that might ultimately lead to mood and behavioral changes.

Microbiom imbalance in neuropsychiatric disorders and Autism: Recent evidences have been accumulated proposing that symbiotic gut microbiota manipulate brain functions in a way that a balanced microbiome can promote mental health [131]. The balanced microbiome fight against many psychological disorders [132,133]. Novel terms such as 'psychobiotics' and 'psychomicrobiotics' are now

being used to highlight the likelihood that gut microbiome imbalance may have adverse impact on mental processes [134]. Microbial imbalance (dysbiosis or dysbacteriosis), can give rise to major psychiatric disorders [135].

Microbiota alterations have been demonstrated to modulate anxiety-like and depression-like behaviors. Similar alterations have been associated to autism [136]. In recent years, the significance of gut microbiome dysbiosis in the pathophysiology of illnesses such as autism, dementia and mood disorders, has been raised. The inflammatory state alteration, induced by a parallel alteration in microbiome structure, is pathognomonic in disorders like schizophrenia, major depressive disorder and bipolar disorder, implicating microbiota in the development of neuropsychiatric illnesses [130].

Recently, it was found that not only gut microbiome dysbiosis that could precipitate neuropsychiatric disorders but also oropharyngeal microbiome. In a recent comprehensive study, researchers have identified a potential link between microbiota inhabiting the throat and schizophrenia. The oropharynx of schizophrenics seems to conceal a composition of oral microbiota different than healthy individuals. Ascomycota and lactic acid bacteria were relatively more abundant in schizophrenics than controls. Healthy individuals were richer in species but less even in their diversity [137].

The fact that the microbiome structure within members of a family has closer similarity than with non-family members [138], is consistent with the familial nature of schizophrenia distribution. Similarly, microbiata composition is more uniform in monozygotic twins than it does in dizygotic ones [139-140]. This finding is once again consistent with the schizophrenia twin studies [141]. Evidences that implicate microbiome dysbiosis in schizophrenia includes structural damage to the gastrointestinal tract, a robust immune response to infectious agents and food antigens, and microbiome changes known in other neuropsychiatric illnesses. Several mechanisms have been proposed to mediate the effect of microbiome imbalance on the development of neuropsychiatric disorders. Modification of intestinal permeability that permits access of endotoxins in the systemic blood could result in alteration of neuronal activity in the limbic system such as increased amygdala activity as well as microglia activation, contributing to chronic inflammation of CNS. Given the assumed anti-inflammatory actions of butyrate, it is likely that dysbiosis may result in depletion of butyrate-producing bacteria thus promoting inflammation. A deviant immune response induced by microbiome dysbiosis could favor the release of relatively excess proinflammatory cytokines. Schizophrenia, major depressive and bipolar disorders are characterized by abnormal profiles of circulating pro- and anti-inflammatory cytokines [136]. Certain abnormalities in neuropeptides and neurotransmitters have been long linked to schizophrenia development. Several reports have shown noticeable alterations in neuropeptides and neurotransmitters in response to changes in the gut microbiome structure. Lactobacillus acidophilus promotes the expression of cannabinoid and opioid receptors in experimental murine models as well as in human epithelial-cell cultures, in that way reducing experimentally evoked pain [142]. Antibiotic-induced microbiome imbalance is correlated with higher concentrations of substance P in the colon [143]. In response to the gut microbiota, the host may also produce an excess of neurochemicals, which help mitigating inflammation, diminishing the stress response, and ultimately improving mood [141,144].

The epidemiological data showed that mothers who experienced high, prolonged fever during pregnancy are up to seven times more probable to give a child that will develop autism. Similarly an increased risk of autism was demonstrated in offspring born to pregnant female monkeys infected with pathogens has recently been confirmed [145]. These data suggested a hypothesis of an early immune activation for autism. However, recent data showed that offspring of mice exposed to premature immune activation and developed behavioral abnormalities, have an altered gut microbiome structure, gastrointestinal abnormalities, and defects in intestinal permeability 'leaky gut' similar to those demonstrated in human cases of autism [146,147]. Thus, microbiome alteration might be one of the mechanisms by which early immune activation mediates development of autism. The microbiome dysbiosis results in a subsequent modification of intestinal permeability that leads to lipopolysaccharide (LPS), pro-inflammatory endotoxin, overproduction and release into the blood modulating specific CNS regions especially those related to the emotions control such as amygdale [148]. It also lead to predominance of pro-inflammatory cytokines that modify the physiological brain activity and modulating the synthesis of neuropeptides [149]. A study [150] has demonstrated significantly higher serum levels of LPS in autistic patients compared to healthy individuals. The possible role of gut microbiota in the pathophysiology of such illnesses has been broadly investigated in animal models. Differences in the gut microbiota between offspring of maternal immune activation mice and controls were detected. The discrepancy was mainly due to the great diversity of Clostridia and Bacteroidia [146]. It has been also demonstrated that a large number of *Clostridium sp.* dominates the microbiome composition of fecal specimens from autistic patients [19,151,152]. An imbalance of Bacteroidetes and Firmicutes phyla,were also detected characterized by a high profile of Bacteroidetes and other gut symbiotics [153]. Another study hypothesized that the alteration of endogenous gut microbiota, in autistic patients, allows other bacteria that are able to generate neurotoxins to colonize the gut and partly contribute to the development of autistic symptoms.

Conclusion

It is plausible that microbial agents with their multifaceted capacity to interact with CNS, are able to precipitate mood and behavior changes. Establishing an infectious basis for neuropsychiatric and neurodevelopmental disorders, is a testable hypothesis that could elucidate the obscure pathophysiology of these illnesses. Better understanding of CNS interactions either with committed pathogens or inhabiting microbiota could shift the clinical classification of refractory disorders such as schizophrenia and autism, to the category of treatable and preventable diseases. Deeper dissection of the immunologic and metabolic pathways involved in brain-microbe interaction might yield a novel array of diagnostic and prognostic laboratory biomarkers of neuropsychiatric/neurodevelopmental disorders. Genuine scientific thinking as well as research approaches that are able to cross classical interdisciplinary boundaries could result in a breakthrough in this field of psychiatric research that, while in its infancy, seems very promising.

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