Review

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Microbiota and neurodevelopmental windows: implications for brain disorders

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Gut microbiota is essential to human health, playing a major role in the bidirectional communication between the gastrointestinal tract and the central nervous system. The microbiota undergoes a vigorous process of development throughout the lifespan and establishes its symbiotic rapport with the host early in life. Early life perturbations of the developing gut microbiota can impact neurodevelopment and potentially lead to adverse mental health outcomes later in life. This review compares the parallel early development of the intestinal microbiota and the nervous system. The concept of parallel and interacting microbial–neural critical windows opens new avenues for developing novel microbiota-modulating based therapeutic interventions in early life to combat neurodevelopmental deficits and brain disorders.

Microbiota–gut–brain axis

Microbes within and on our bodies are a thriving dynamic population forming a symbiotic superorganism. The collective comprises a myriad of bacteria, of approximately 10^{14} cells, containing 100 times the number of genes of the human genome [1]. Despite the evolution of this microbiome (see Glossary) for 500 million years [2,3], it is only recently that advances in sequencing technology have allowed us to appreciate the full nature of the complexities of host–microbe relationships. The largest microbial component of the human microbiome is located in the large intestine of the gastrointestinal (GI) tract. It is now clear that the gut microbiota plays a key role in the life and health of the host by protecting against pathogens, metabolizing dietary nutrients and drugs, and influencing the absorption and distribution of dietary fat [2]. However, the influence of the microbiota extends beyond the GI tract, playing a major role in the bidirectional communication

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Glossary

Alzheimer's disease: a progressive age-associated neurodegenerative disorder characterized by cognitive decline and build-up of protein 'plaques' and 'tangles' in the brain.
Astrocytes: the most abundant glial cell of the human brain, providing support for the blood–brain barrier, provision of nutrients to the nervous tissue, and a role in the repair and scarring process of the CNS following traumatic injuries.
Attention deficity hyperactivity disorder (ADHD): a psychiatric disorder usually occurring in childhood characterized by significant attention problems, hyperactivity, or impulsivity.
Autism: a neurodevelopmental disorder characterized by the presence of stereotypical behavior and communication and social interaction deficits, with a male gender bias.
Brain–gut axis: a complex network of communication between the gut and the brain, which modulates the GI tract and CNS, playing an important role in maintaining homeostasis.
Cortical neurogenesis: the generation of new neurons in the cerebral cortex.
Dysbiosis: a microbial imbalance on or within the body, often localized to the gut.
Gliogenesis: the generation of new glial cells.
Irritable bowel syndrome: a disorder of the brain–gut axis. In addition to GI symptoms, irritable bowel syndrome is also associated with frequent comorbidities of depression and anxiety.
Hippocampal neurogenesis: a process by which neurons are generated in the hippocampus.
Leaky gut: an increase in the permeability of the intestinal mucosa, allowing bacteria and toxins to leak into the bloodstream (Box 2).
Microbiome: the collective genomes of all the microorganisms in a microbiota.
Microbiota: the entire microbial population residing in particular parts of the body, such as the intestine or skin.
Mood disorders: a constellation of mental disorders encompassing major depression and bipolar disorder (combining episodes of both mania and depression).
Neurodevelopment: the development of the CNS system, occurring mostly in prenatal and early life.
Neurulation: a key neurodevelopmental event that begins the genesis of the nervous system by 'folding' the embryonic nervous system to form the neural tube.
Schizophrenia: a mental disorder characterized by positive (hallucinations and delusions) and negative (anhedonia, social withdrawal) symptoms, which typically emerge in adolescence and early adulthood.
Short chain fatty acids (SCFAs): bacterial products or metabolites from the fermentation of dietary carbohydrates in the gut, which have immunomodulatory properties and can interact with nerve cells by stimulating the sympathetic nervous system.
Synaptic pruning: a process where synapses are eliminated during neurodevelopment and/or aging.
Systems matching: a process that refines neuronal numbers to match the requirements of the neural circuit which they become part of.

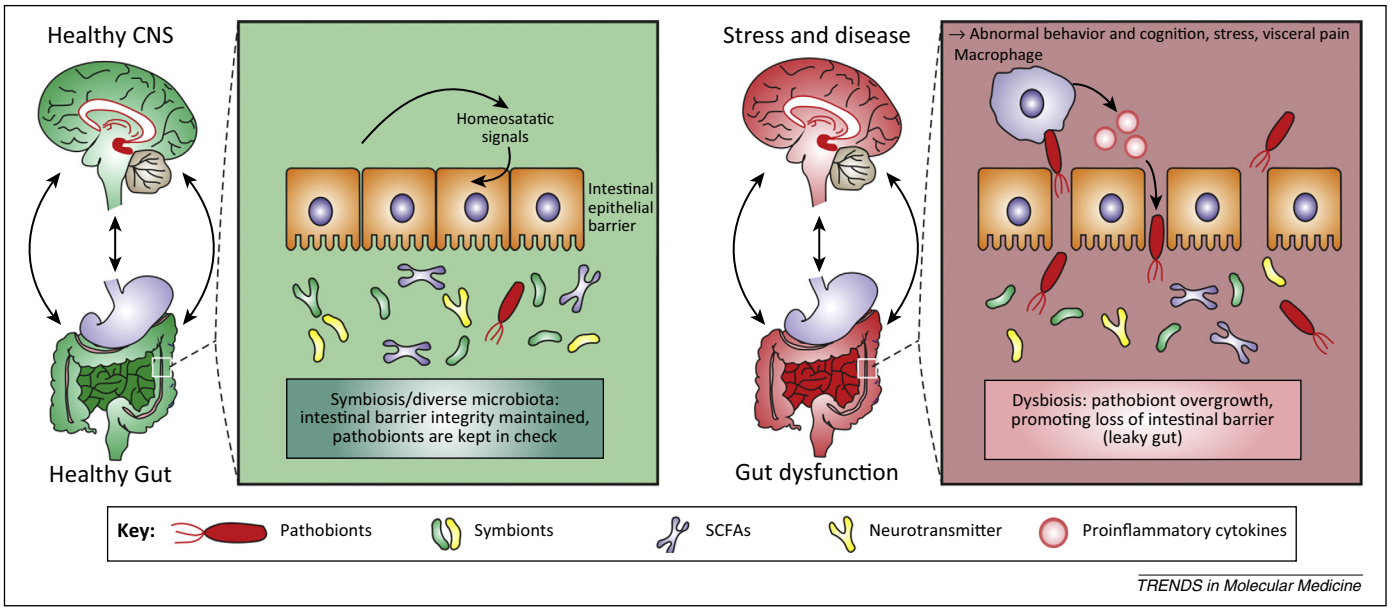

Figure 1. Microbiota–gut–brain axis communication in health and disease. (Left) Under healthy conditions, the predominance of symbiotic bacteria, an intact intestinal barrier, a healthy innate immunity controlling pathobiont overgrowth inside the intestinal tract and healthy gut function support the symbiotic relationship between CNS function and gut microbiota. (Right) Under pathological stress and/or disease conditions, intestinal dysbiosis can adversely influence gut physiology leading to inappropriate brain–gut axis signaling and associated consequences for CNS functions and disease states. Stress at the level of the CNS can also impact on gut function and lead to perturbations of the microbiota. A change in the balance of symbionts and pathobionts favoring pathobiont overgrowth results in dysbiosis, which can induce inflammation. During inflammatory responses, macrophages contribute to pathogenesis through inappropriate responses to enteric microbial stimuli, inefficient clearance of microbes from host tissues, and impaired proinflammatory and anti-inflammatory responses, and loss of barrier function (leaky gut; see Box 2). This promotes the increased translocation of pathogenic bacterial components from the intestinal mucosa to the systemic circulation, where they activate innate immunity, characterized by production of proinflammatory cytokines, resulting in systemic inflammation and abnormal gut function. These mechanisms potentially lead to impaired CNS function such as altered neurochemistry, cognition, behavior, stress response, and visceral pain. Abbreviations: CNS, central nervous system; SCFAs, short chain fatty acids.

between the GI tract and the central nervous system (CNS) [4] (Figure 1).

The concept of the brain–gut axis emerged in the 19th and early 20th centuries from the pioneering observations of Beaumont, Darwin, and Cannon in tandem with the now classical physiological studies of Ivan Pavlov [4,5]. More recently, given the realization of the importance of the microbiota in modulating health, the brain–gut axis has been extended to the microbiota–gut–brain axis [6–8], which represents a complex network of communication between the gut, the intestinal microbiota, and the brain, modulating immune, GI, and CNS functions [6,9]. It encompasses the CNS, the sympathetic and parasympathetic branches of the autonomic nervous system, as well as the enteric nervous system and the neuroendocrine and neuroimmune systems [10]. In healthy individuals, the normal dominant microbiota is relatively stable and forms a mutually beneficial rapport with the host. However, perturbations in the delicate synergetic host–microbiota relationship may have serious consequences and has the potential to exacerbate brain, digestive, and metabolic disorders [9–14] (Figure 1). For example, bidirectional communication between the microbiota and the CNS influences stress reactivity, pain perception, neurochemistry, and several brain–gut axis disorders [4,7,15]. Despite several investigations focusing on the exploration of the bidirectional communication between the microbiota and the CNS, more is known about gut microbiota modifying CNS (Box 1), whereas the mechanisms by which the CNS can modify gut microbial communities remain to be fully elucidated.

In addition to neural, endocrine, and metabolic pathways, immunological mechanisms may be an additional mechanism in signaling with the potential to affect neurodevelopment. Leaky gut (Figure 1 and Box 2) as the result of dysbiosis offers an alternative mechanism of inducing an immune response, and the phenotypic changes of immune cells induced by gut microbes may modulate the neurodevelopment–microbiota interaction.

The dynamics of the various endogenous and exogenous factors, which may have a profound effect on the microbiota composition leading to dysbiosis and impacting multiple human pathologies, from metabolic syndromes to mental disorders are slowly being unraveled [16]. The microbiota undergoes a vigorous process of maturation and development throughout lifespan and establishes its mutually beneficial cohabitation with the host during life. The composition of the gut microbiota during critical periods of CNS development is affected by a broad range of factors. Perturbation of any of these factors can lead to host stress or disease (Figure 1).

Shaping of the microbiota occurs in parallel with neurodevelopment and they have similar critical developmental windows (Figure 2) sensitive to damage. Recently, the microbiota–gut–brain axis emerged as a key player in neurodevelopmental phases, indicating that early-life events during initial colonization and microbiota development can determine general and mental health in later life [17,18]. Importantly, childhood and adolescence are the most dynamic periods of change in relation to microbiota and brain development. Thus, disruptions during such critical periods of dynamic microbiota–host interaction have the potential to profoundly alter brain–gut signaling, affect health throughout life, and increase the risk of (or lead to) neurodevelopmental disorders.