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Mammalian gut microbiome and brain development: A comprehensive review

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ABSTRACT

Both internal and external environmental cues during prenatal life have been shown to play an important role in mammalian brain development. Epidemiological data have indicated a possible common link between neurodevelopmental disorders, such as autism and schizophrenia, and microbial pathogen infections during the prenatal period. The gut is exposed to a wide range of external influences due to its extensive surface area. By working alongside the beneficial microbes in the gut, the brain efficiently processes the large volume of chemical signals that enter the gut daily. Most bacteria in mammals are located in the colon. Given their presence in the mammalian body for millions of years, it is plausible that microbes have co-evolved with the animals. Recent environmental studies have delved into the hypothesis of the microbiota-gut-brain axis to elucidate the impact of the gut microbiota on the mammalian brain. Certain components of the bacterial cell wall have the ability to traverse the placenta and reach the brain. Toll-like receptor two activation leads to increased expression of transcription factors that regulate development and neurogenesis. Research has revealed a new connection between the effects of cytokines produced by microbiota-controlled microbial activity and the neurogenesis process. This review explores the influence of gut microbiome (GM) on mammalian neurogenesis, myelination, and the blood-brain barrier. The findings support the conclusion that GM impacts the behaviors of neural stem cells and neurogenesis, which is essential for mammalian brain development. Moreover, disturbances in gut microbiota can lead to abnormal neurogenesis and mammalian brain mal-development.

Keywords: Gastrointestinal microbiome, Mammalian brain development, Neurogenesis, Neural stem cells.
Article type: Research Article.

INTRODUCTION

The animal gut microbiota, comprising a diverse array of microorganisms, plays a pivotal role in shaping host health and physiology. Environmental cues during prenatal life have been demonstrated to be important in animal organ development. Epidemiological data have indicated a possible common link between neurodevelopmental disorders, such as autism and schizophrenia, and microbial pathogen infections during the prenatal period (Al-Asmakh *et al.* 2012). The terms microbiota and microbiome have been documented in scientific literature since at least 1927 and 1949, respectively (Farré-Maduell & Casals-Pascual 2019). Theodor Escherich, an Austrian pediatrician, first observed a bacterium (*Escherichia coli*) in the intestinal flora of both healthy children and those with diarrheal disease. Over the following years, more microorganisms were discovered within the human body. For example, in 1898, *Veillonella parvula* was found in the oral, digestive, urinary, and upper respiratory tracts. Bifidobacteria were also reported as part of the intestinal flora in the 1900s. During the 20th century, microorganisms were consistently discovered in nasal passages, oral cavities, skin, the gastrointestinal tract, and the urogenital tract and identified as part of the human microbiota (Hayes & Sahu 2020). Collectively, these microorganisms form a complex known as the microbiome. The genetic material that makes up the animal microbiome encompasses a wide variety of organisms, including bacteria, archaea, fungi, protozoans, and nonliving viruses, predominantly located in the gastrointestinal tract. Bacteria are the most abundant components

of the human microbiome: estimates suggest that there are 75 to 200 trillion individual bacterial organisms. In contrast, the human body as a whole consists of roughly 50 to 100 trillion somatic cells. The human gut microbiome's diversity rises from birth to childhood, remains fairly constant during adulthood, and then starts declining as individuals age (Sender *et al.* 2016). The microbiota are collections of various microorganisms present in the bodies of multicellular organisms, including the vertebrates. Research on human microbiota began in the late 19th century and has progressed significantly through the Human Microbiome Project (HMP), an international initiative focused on identifying the types and functions of microorganisms in humans. To date, it has been demonstrated that human microbiota, particularly those residing in the intestinal tracts, impact multiple facets of human well-being, such as the development of organs, metabolism, immunity, neural functions, and the aging process. The imbalance of the microbiota can lead to the disruption of bodily processes and the development of conditions like cardiovascular diseases (CVDs), cancer, autism, dementia, inflammatory bowel disease (IBD), and respiratory illnesses. Moreover, several brain disorders, including Parkinson's disease, neurodegenerative diseases, depression, stress, Alzheimer's disease, and neurodevelopmental disorders, have been linked to altered gut microbiota or gut dysbiosis (Chen *et al.* 2021; Fig. 1). Some microorganisms are harmful, while others are helpful or necessary for human health (Griffith & Morgan 2019; Mashayekhi & Salehi 2024).

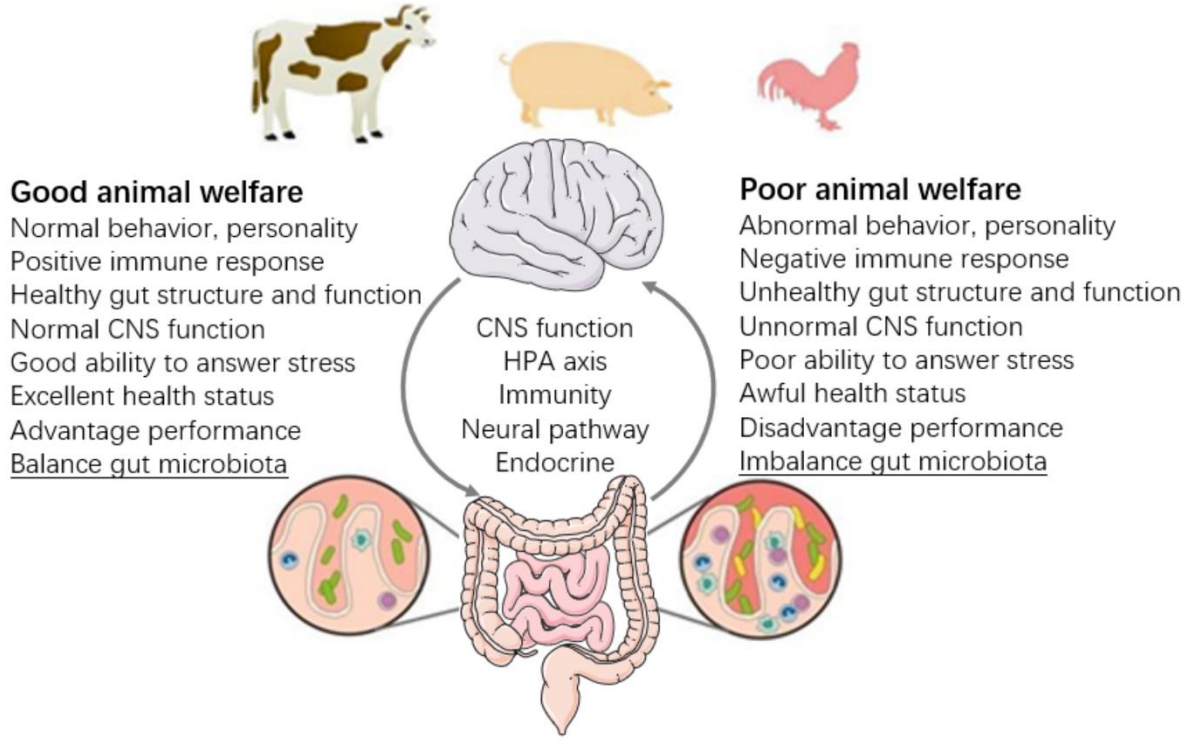

Fig. 1. Animal welfare in the implication and perspective of the gut microbiome (Chen *et al.* 2021).

Microbiota and organ development in mammals

Microorganisms have significantly impacted the evolution of eukaryotes. Host-microbe interactions can be advantageous, such as assisting with host nutrition or protecting against pathogens and predators (Sonnenburg & Bäckhed 2016). Microbiota also influence various host developmental processes, including those related to the vertebrate digestive and immune systems and the light organ of the Hawaiian bobtail squid (McFall-Ngai 2014). The host-microbiome supraorganism seems to have co-evolved, potentially influencing the development of evolving traits in all life forms on this planet, which is largely microbial. It appears that the microbiota can impact the subsequent generation from pregnancy through maternal microbiota and immune responses. The microbiota ecosystems are observed to grow within their epithelial habitats due to the host immune system, synchronously with the host's chronological growth, offering early adjustments to the physiological development and functions of the host for nutrition, immunity, and defense against pathogens at all stages of life (Dominguez Bello 2019). The phenotype of an organism is not solely determined by the material within a fertilized egg. Instead, the inherited genome creates a developmental system capable of responding to various environmental factors. Normal

development requires chemical signals from symbionts, typically bacteria or fungi. In mammals, acquiring the gut microbiome at birth is crucial for developing the gut, the capillary network the immune system and the normal development of the brain. Furthermore, for normal development, abiotic factors like temperature can be crucial. The sex of many non-mammalian vertebrates is determined by the temperature they encounter during development. Additionally, biotic factors such as diet or the existence of predators can modify development to make the phenotype more adaptable. The organism's ability to respond to environmental cues can assist it in integrating into its habitat (Watts *et al.* 2022). Having a healthy microbiome is essential for the normal development of animals. The population of microbes in and on our bodies relies on the same enzyme that glyphosate inhibits, and they can also be harmed by this "herbicide." As a result, a new area of teratology has emerged, focusing on developmental defects caused by a chemical's ability to eliminate the bacteria that provide signals for normal development (Aitbali *et al.* 2018). *Aeromonas*, a less common member of the microbiome, is essential for the normal growth of insulin-producing beta cells in the pancreas of zebrafish (Hill *et al.* 2016). Within this bacterial species lies a gene called *BefA*, which produces a protein that encourages the growth of beta cells in zebrafish from their embryonic to adult stages. Zebrafish that lack *Aeromonas* (or have *Aeromonas* bacteria without this gene) have limited beta cells. However, the wild-type *BefA* gene protein can restore the beta cell count to normal levels in these fish. Zebrafish with low beta cell counts experience symptoms resembling diabetes. The presence of the *BefA* protein produced by gut microbes in humans has led scientists to speculate about the potential connection between childhood gut microbiome diversity and diabetes in certain individuals (Shin *et al.* 2022).

Gut microbiome and brain development

The body's gut is vast and exposed to various external influences. The brain collaborates with beneficial microbes in the gut to effectively manage the large volume of chemical signals that enter the gut daily. The intestinal microbiota also facilitates the development of the enteric nervous system. Mice that are free of germs display physiological and structural irregularities and struggle with generating peristalsis in their digestive tract (Collins *et al.* 2014). Symbiotic bacteria play a critical role in developing gut lymphocytes and neurons in mammals. Evidence suggests that symbiotic bacteria play a role in stimulating the postnatal development of the mammalian brain (Sharon *et al.* 2016). Germ-free mice display lower levels of the transcription factor *Egr1* and the paracrine factor brain-derived neurotrophic factor (BDNF) in relevant areas of their brains compared to conventionally raised mice. Additionally, germ-free mice have higher levels of the neural hormone serotonin (Clarke *et al.* 2013). The differences in behavior observed in groups of mice are related to the idea that during the process of evolution, the establishment of gut microbiota has become intertwined with the programming of brain development, impacting both motor control and anxiety-like behavior. A specific study found that a particular *Lactobacillus* strain can influence emotional behavior by regulating GABA receptors through the vagus nerve (Bravo *et al.* 2011). This suggests that there could be pathways through which bacterial products enter the bloodstream and contribute to regulating brain development. Many studies show that the microenvironment around neural stem cells plays an important role in regulating their behavior (Mashayekhi *et al.* 2002, Owen-Lynch *et al.* 2003). Emerging evidence indicates that neurotrophins and neurotransmitters produced by the gut microbiome may interact with complex survival and differentiation pathways in different brain areas, influencing the behavior of neural stem cells. The relationship between synaptic growth and maturation, as well as the plasticity and development of neurons is well-established. The administration of prebiotic immunogen has been shown to improve the growth performance and survival rate of *Rutilus kutum* fry (Keramat Amirkolaie 2015). When neonatal prebiotics were administered to 22-day-old mice, higher levels of synaptophysin and BDNF were observed in the hippocampus compared to other prebiotics (Ratsika *et al.* 2023). Both BDNF and synaptophysin, which are synaptic vesicle proteins, serve as signaling molecules that aid in the formation of neuron-to-neuron connections and are essential for the survival, growth, maturation, and maintenance of various brain cell populations (Nasseri *et al.* 2024). The gut microbiome releases serotonin, a neurotransmitter and signaling molecule, into the gut lumen, thereby promoting the growth of new neurons in adult organisms. Furthermore, studies have demonstrated that the gut microbiome plays a significant role in serotonin signaling pathways, impacting various brain areas. Multiple research findings have also indicated the gut microbiome's influence on regulating adult neurogenesis. Evidence has revealed that the absence of microorganisms results in an abnormal rise in adult dorsal hippocampus neurogenesis. Moreover, the study found that microbial signals affected the generation of new neurons in the hippocampus during the critical early life period (Lynch *et al.* 2023). The gut microbiota's involvement in the early development of the brain could contribute to the transmission of microbiota.

Research has yielded strong evidence to support the idea that bacteria actively contribute to developing and advancing the central nervous system (CNS). The importance of gut microbiomes in various neurodevelopmental processes has become increasingly apparent. These processes encompass myelination, the formation of the blood-brain barrier (BBB), neurogenesis, and the maturation of microglia, all of which significantly influence animal cognition and behavior (Sharon *et al.* 2016). It has been suggested that early-life gut microbiota may be associated with behavioral and cognitive development (Willemsen *et al.* 2024). The development of neuronal cells and the optimal functioning of the growing body necessitate a range of nutrients released by the gut. In addition, recent research indicates that the gut microbiome (GM) could directly improve brain development processes, resulting in long-term health advantages. Moreover, the formation of new functioning neurons, known as neurogenesis, may be involved in the transmission of genetic material during the brain development of newborns. This process occurs through the differentiation of neural stem and progenitor cells. Neurogenesis and neuronal plasticity are crucial for learning, memory, cognition, and stress response and are particularly prevalent in the hippocampus, which is central to cognitive activities. Sarubbo *et al.* detail how maintaining a well-balanced microbiota in the colon could impact the microenvironment, stimulating neuronal growth (Sarubbo *et al.* 2022). The comparison between mice lacking a GM (germ-free mice) and mice with a regular GM (specific pathogen-free mice) in a study revealed that various substances produced by the GM can travel through the placenta and reach the developing fetus, thereby impacting its growth and development. Peptidoglycan (PG), a component found in bacterial cell walls, can penetrate the placenta and reach the developing baby's brain. This activates Toll-like receptor 2, leading to an increase in the expression of *FOXG1*, a crucial transcription factor that controls the development and formation of neurons. Consequently, there is an increase in neuron growth in the forebrain. The relationship between the effects of cytokines produced by microbiota-mediated microbial activity and the process of neurogenesis has been elucidated (Salvo *et al.* 2020, Tiwari *et al.* 2021).

Effects of GM on neurogenesis and neural stem cell

The growth of new functional neurons from neural stem/progenitor cells is known as neurogenesis. Neurogenesis and neuronal plasticity play a crucial role in learning, memory, cognition, and stress response, particularly in the hippocampus, which is the center of cognition (Kempermann 2019). A well-balanced gut microbiota is directly or indirectly involved in creating the right conditions to support neuronal development (Sarubbo *et al.* 2022). Compared to control mice, germ-free (GF) mice display heightened adult hippocampal neurogenesis, but this effect is only observed in the dorsal hippocampus, which is essential for spatial learning and memory. Furthermore, there is an essential early developmental stage during which microbiota colonization impacts adult hippocampal neurogenesis. Genes related to myelination and myelin plasticity were found to be upregulated in the prefrontal cortex of GF mice (Hoban *et al.* 2016). In addition, the changes in myelin and activity-related gene expression in the prefrontal cortex were reversed upon recolonization with conventional microbiota. Since the prefrontal cortex is implicated in neuropsychiatric disorders like attention deficit hyperactivity disorder, Autism spectrum disorder (ASD), depression, and schizophrenia, it is important to explore the connection between gut bacteria and these conditions. Additionally, GF mice showed altered expression of genes related to synaptic plasticity, as reported by Stilling *et al.* (2015). Most neurons and neuroendocrine cells express synaptophysin, a glycoprotein found in synaptic vesicles, making it an indirect indicator of synaptic plasticity in the brain. It has been suggested that gut bacteria play a role in regulating the expression of synaptophysin and postsynaptic density protein 95 (*PSD*-95), which is crucial for the maturation of excitatory synapses (Wang *et al.* 2024). The gut microbiota also contributes to the development of microglia, the brain's main immune cells. Microglia play various roles in brain development, such as synaptic patterning, cell genesis, myelinogenesis, cell positioning, cell survival, axon dynamics, and cellular phagocytosis. It has been observed that disruptions in the gut microbial community can affect the development of microglia. According to Erny *et al.*, mice that are germ-free (GF) or treated with antibiotics exhibit changes in the microglial ratio and an immature phenotype (Erny *et al.* 2015). Replenishing the gut microbiota and short-chain fatty acids (SCFAs), which are bacterial fermentation products containing acetic propionic acid and butyric acid, can restore defective microglia—adding the SCFA mixture to the drinking water of GF mice for 4 weeks normalized microglial density in cortical specimens (Matcovitch-Natan *et al.* 2016). It has been demonstrated that various metabolites from gut microbes can traverse the placenta into the fetal compartment and have the capacity to induce and control the prenatal developmental process (Pessa-Morikawa *et al.* 2022). Moreover, peptidoglycan (PG), a constituent of the bacterial cell wall, traverses the

placenta to access the fetal brain, where it activates Toll-like receptor 2 (TLR2), leading to an upregulation of *FOXG*1 expression, a critical transcription factor involved in regulating development and neurogenesis, thus prompting the proliferation of neurons in the forebrain region (Kaul *et al.* 2012; Humann *et al.* 2016). A recent investigation presents direct proof linking the manipulation of microbial function and associated cytokines by the microbiota to influence the process of neurogenesis (Salvo *et al.* 2020). In addition, gut bacteria indirectly influence the adaptability of neurons by controlling the movement and development of neurons in the central nervous system, possibly through the regulation of ephrin B and reelin pathway. Ephrin B is essential for maintaining the integrity of the gut epithelial barrier, while reelin, a membrane glycoprotein, is responsible for neuronal movement (Hemmati *et al.* 2014; Allam-Ndoul *et al.* 2020,). Increasing evidence indicates that gut microbes can alter the future of neural stem cells by interacting with complex pathways involved in differentiation and survival through neurotrophins and neurotransmitters in various brain regions (Sharon *et al.* 2016). The development and maturation of synapses are linked to the maturation and adaptability of neurons. Studies have shown that administering neonatal prebiotics (BGOs) can increase the expression of synaptophysin and BDNF in the hippocampus. Synaptophysin is a protein found in synaptic vesicles that regulates the kinetics of synaptic vesicle endocytosis. BDNF is a growth factor produced by neurons that serves as a signaling molecule for various brain cell populations' survival, growth, and maintenance (Salehi & Mashayekhi 2009; Williams *et al*. 2016). Additionally, serotonin can be produced and released by gut microbes into the gut lumen, and it is known to support adult neurogenesis (Alenina & Klempin 2015). In addition, the use of antibiotics, which has a detrimental effect on gut microbiota, has been linked to reduced neurogenesis (Möhle *et al.* 2016). The gut bacteria support the enteric nervous system in adult mice by promoting neurogenesis through Toll-like receptor 2 (Yarandi *et al.* 2020). Moreover, the microbiome indirectly impacts hippocampal neurogenesis by regulating the neuronal immune system (Salvo *et al*. 2020). Early life stress, such as lack of social interaction, can also disrupt the stability of the gut microbiome (Glover *et al.* 2018), leading to decreased neurogenesis and IL-6 levels in the hippocampus of socially isolated mice (Dunphy-Doherty *et al.* 2018). Reduced hippocampal neurogenesis is closely linked to impaired learning, anxiety, depressive-like behaviors, and neuroinflammation, all of which also have a clear association with structural changes in the gut microbiome (Liu *et al.* 2022). The brain's development and normal functioning are closely linked to the formation and activation of neuron and glial cells. This process is also associated with the differentiation of neural stem cells (NSCs). NSCs are a type of precursor cells with the potential to differentiate in multiple directions and the ability to renew themselves. They can multiply and differentiate into neurons, astrocytes, and oligodendrocytes during embryonic development or in the adult brain. However, NSCs remain inactive long after the embryonic stage (Bottes *et al.* 2021). Research has shown that the microbiota in the gut has a significant impact on the regulation of neuronal and glial function. They influence the cytogenesis and activation of neurons and glial cells through the microbiota-gut-brain (MGB) axis (Fig. 2), which includes the enteric nervous system, central nervous system, and the immune system (Gershon & Margolis 2021; Basiji *et al.* 2023). Through their metabolites, the gut microbiota establishes two-way communication with the brain by crossing the blood-brain barrier (BBB), traveling through the vagus nerve, or triggering peripheral immunity (Morais *et al.* 2021). As a result, changes in the gut microbiota composition can impact the differentiation of neural stem cells and neurogenesis. Traditional Chinese Medicine (TCM) has a rich history as a medical system and is extensively employed in preventing and treating nervous system ailments and maintaining body balance. TCM's active components are crucial in controlling the differentiation of NSCs and the generation and activation of neurons and glia (Wang *et al.* 2021). Several studies have suggested that TCM can influence the gut microbiota's composition and metabolism (Feng *et al.* 2019). The gut microbiota has the ability to release signaling molecules that support the function of the host's digestive, immune, metabolic, and neurobiological systems, and these molecules can also be influenced by medication. TCM has demonstrated significant potential in regulating the gut microbiota to impact neural stem cells. Within the neurogenic niches, the proliferation, differentiation, and movement of NSCs uphold neurogenesis through interactions with glial cells, the extracellular matrix, and the niche's microenvironment. Changes in NSC function can be influenced by alterations in the cell, ECM, and microenvironment components, which can modify external factors and impact relevant signaling pathways such as Notch, Wnt, SHH, FOXO, and other proteins or factors, ultimately affecting neurogenesis. Thus, fluctuations in the abundance of gut microbiota could result in neurogenesis by modifying cells, the ECM, and microenvironmental components in specific manners. The Notch pathway regulates NSCs at various developmental stages during brain development in both embryos and adult animals, maintaining the NSC count

in the brain. The Wnt/β-catenin signaling pathway primarily participates in NSC proliferation and differentiation. The SHH pathway also plays a crucial role in neurogenesis (Zhang *et al.* 2022).

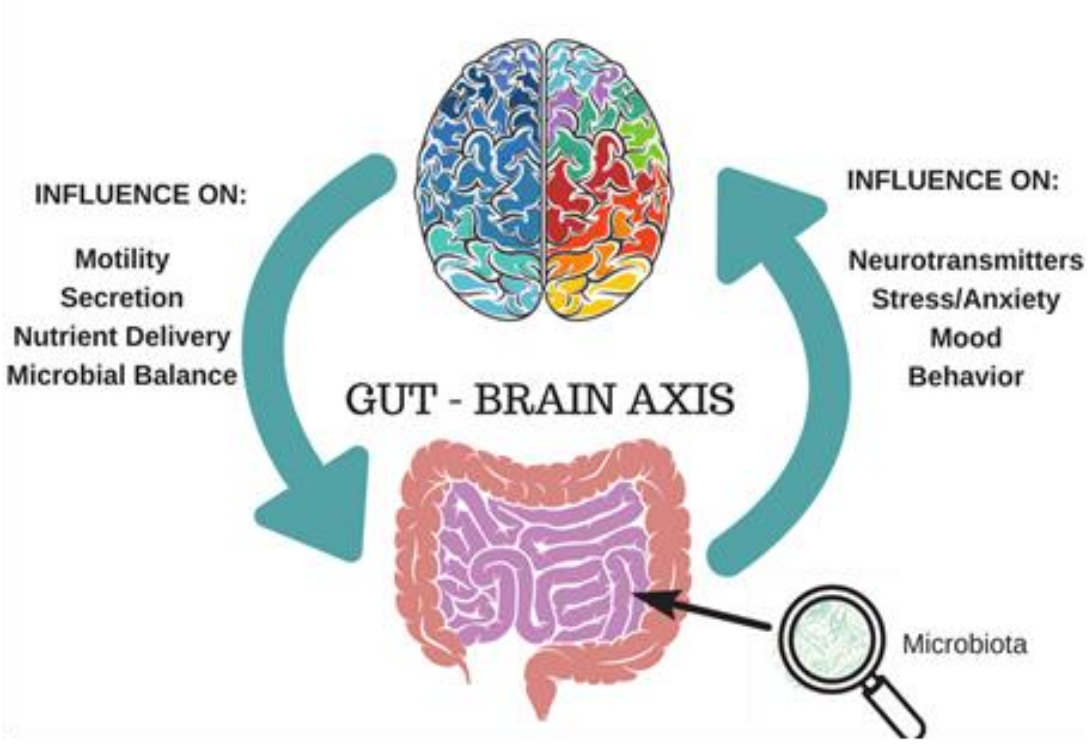

Fig. 2. The brain and gut have bidirectional influence on each other (Microbiota-gut-brain axis). Animal brain can influence on motility, secretion, nutrient delivery and microbial balance, while gut microbiome influences on neurotransmitter, mood, and behavior (Mayer *et al.* 2014).

Given that changes in the gut microbiota can result in abnormal neurogenesis and neural stem cell functioning, there may be potential to influence the gut microbiota in brain conditions associated with abnormal myelin formation, synapses, or microglia.

Impact of GM on blood-brain barrier

The microvasculature of the CNS is termed the blood-brain barrier (BBB) due to its unique properties. These CNS vessels are continuous and nonfenestrated, with additional properties that tightly regulate the movement of molecules, ions, and cells between the blood and the CNS (Daneman 2012). The BBB consists of a thin monolayer of brain endothelial cells in close contact with vascular cells (pericytes and vascular smooth muscle cells), glial cells (astrocytes, microglia), and neurons. These components' communication and molecular signaling are collectively called the neurovascular unit (Banks 2016). The BBB is established during early in-utero development, with capillary endothelial cells being sealed by tight junction proteins, pericytes, and astrocytes to create a restrictive barrier between the brain and systemic circulation. Additionally, it enables the exchange of molecules and nutrients necessary for the proper functioning and maintenance of the brain (Braniste *et al.* 2014). An increasing body of research indicates that gut microbes play a significant role in maintaining BBB integrity. Studies have shown that germ-free (GF) mice have increased BBB permeability in various brain regions such as the frontal cortex, hippocampus, and striatum. It has been discovered that well-balanced gut microbiota and microbial-derived metabolites, such as SCFAs, are crucial for regulating the formation and upkeep of a healthy BBB (Michel & Prat 2016). The permeability of the BBB decreases as sterile fetuses develop into adulthood. In mice without germs (GF mice), the permeability of the BBB increases for larger molecules because there is reduced expression of essential junctional proteins, Occludin and Claudin-5 in the brain's endothelial layer. Studies have demonstrated that microbial colonization of the gut or the introduction of butyrate, a SCFA produced by microbial fermentation in the gut, can reduce the permeability of the BBB in GF mice. The gut microbiome improves postoperative cognitive function by decreasing the permeability of the blood-brain barrier in aged mice

(Braniste *et al.* 2014). The results show that the gut microbiota plays a crucial role in the BBB, but the exact mechanism still needs to be understood. Ongoing studies indicate that the gut microbiota influences the BBB through different pathways, including the vagus and sympathetic nerves, immune and endocrine systems, and intestinal microbial products like SCFAs and lipopolysaccharides (LPS; Powell *et al.* 2017).

GM and myelin synthesis

The CNS relies on specialized glial cells called oligodendrocytes for myelination, which involves integrating neurons and building the myelin lipid bilayer (Sharon *et al.* 2016; Ntranos & Casaccia 2018). When born, humans have mostly unmyelinated axons, and rapid myelination by oligodendrocytes [Oligodendrocyte transcription factor 2 (Olig2) expressing cells] occurs in the first few years of life (Williamson & Lyons 2018). The activity of oligodendrocytes is influenced by the expression of myelin-related genes (Olig1, Olig2, Mbp, Mog, Opalin; Mashayekhi *et al.* 2015). While the total myelin content and myelination rate vary over time, myelination persistently occurs in an organized spatiotemporal manner into the fourth decade of life to ensure efficient circuit conduction. The regulation of myelination is crucial as it is linked to brain plasticity and function (Almeida & Lyons 2017; Williamson & Lyons 2018). Recent studies have unveiled a direct connection between shifts in myelin-related gene expression and protein levels in the hippocampus of neonates and changes in gut microbiome during infancy, suggesting a causal relationship (Kambe *et al.* 2024). The essential role of the microbiota in myelination and the maintenance of myelin plasticity has been demonstrated through germ-free (GF) mice. The social behavior of mice was negatively affected by dysregulated myelination in the prefrontal cortex (PFC) after fecal transplantation in GF mouse studies (Gacias *et al.* 2016; Hoban *et al.* 2016; Sharon *et al.* 2016). However, the mechanism by which the gut microbiota played a role in these studies still needs to be established. Studies have shown that SCFAs, bacterial metabolites, can have a beneficial impact on stress-induced behavioral deficits and intestinal barrier dysfunctions (Van de Wouw *et al.* 2018) and can influence myelination in the PFC region of the brain (Gacias *et al.* 2016), indicating a potentially new pathway through the MGB axis. It was found that a healthy gut microbiome can impact the process of myelination (Needham 2024). When humans are born, their central nervous system (CNS) primarily consists of unmyelinated axons. As maturing axons develop, they undergo rapid myelination by oligodendrocytes within a few years after birth. This process involves engagement and ensheathment and results in varying rates of myelination and myelin content until early adulthood (Williamson & Lyons 2018). Any disruptions in this process may lead to long-term impairments. Myelination greatly influences cognitive function, and the extent of myelination has been associated with neuronal plasticity and function (Almeida & Lyons 2017). The microbiota in the gut plays a crucial role in controlling myelination by influencing the expression of genes related to myelination in oligodendrocytes. Abnormalities in myelin can adversely affect brain function and behavior (Ntranos & Casaccia 2018). The PFC area of the brain, particularly vulnerable to external influences during the early stages of infantile life, undergoes myelination later, putting it at risk of factors such as intestinal dysbiosis (Hoban *et al.* 2016). Research involving GF mice has demonstrated that irregular myelin development in the PFC region can have detrimental effects on social behavior (Gacias *et al.* 2016). In addition, it has been shown that bacterial byproducts like SCFAs can positively affect stress-related behavioral issues, intestinal barrier problems, and myelination process regulation (Van de Wouw *et al.* 2018). Researchers found that giving SCFA butyrate orally to antibiotic-treated mice led to the recovery of myelination impairments, intestinal health, and behavioral deficits, indicating the vital role of gut microbiota in shaping the MGB axis by regulating myelination in the PFC region (Keogh *et al.* 2021). Therefore, the microbiota plays a crucial role in myelination and the upkeep of myelin sheath plasticity.

CONCLUSION

A bidirectional communication network characterizes the relationship between our CNS and the microbiome ecosystem. Overdoses of antibiotics can disrupt the simultaneous coordinated process of neuronal and gut microbiome development, leading to an inflammatory state during critical brain development phases. The brain collaborates with friendly gut bacteria to effectively process the large chemical signals entering the gut daily. Understanding the connection between the gut microbiota and the brain is crucial for advancing our knowledge of brain development and behavior. There is a connection between the effects of cytokines produced by microbiota-controlled microbial activity and the neurogenesis process. This analysis explores the gut microbiome's influence on neurogenesis, myelination, and the blood-brain barrier. The findings support the

conclusion that GM impacts the behaviors of neural stem cells and neurogenesis, which is essential for mammalian brain development. Moreover, disturbances in the gut microbiota can lead to abnormal neurogenesis and brain mal-development. Additional research is necessary to clarify the particular molecular signaling pathways linked to brain development and the creation of personalized microbiome treatments.

Authors' contributions

Both authors (Farhad Mashayekhi and Zivar Salehi) wrote the manuscript. The authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The author declares that he has no competing interests. The authors declare that they have no support from any organization for the submitted work and no financial relationships with any organizations. They work as researchers at the university.

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