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THE GUT–BRAIN AXIS IN AUTISM SPECTRUM DISORDER: MICROBIOTA, IMMUNE DYSREGULATION, AND THERAPEUTIC PERSPECTIVES

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ABSTRACT

Background: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by persistent difficulties in social communication, restricted and repetitive behaviors, and a high prevalence of co-occurring gastrointestinal, metabolic, and immune disturbances. Increasing evidence suggests that the gut–brain axis—a bidirectional communication network linking intestinal microbiota, immune signaling, metabolic pathways, and neural circuits—may play an important modulatory role in ASD-related neurodevelopmental processes.
Scope: This review synthesizes current evidence on gut–brain axis physiology and examines how alterations in microbiota composition and function intersect with immune dysregulation, microbial metabolite signaling, and neurodevelopment in ASD. Findings from clinical studies, preclinical mechanistic research, and emerging microbiota-targeted therapeutic approaches are integrated to provide a systems-level perspective on microbiota–immune–brain interactions.
Key Findings: Individuals with ASD frequently exhibit altered gut microbial diversity and composition, accompanied by functional disruptions in microbial metabolite pathways, including short-chain fatty acid and tryptophan metabolism. These changes are associated with impaired intestinal barrier integrity, systemic immune activation, neuroinflammatory signaling, and microglial dysfunction, processes that may contribute to excitatory–inhibitory imbalance and altered synaptic plasticity in the central nervous system. Microbiota-targeted interventions—such as probiotics, dietary modification, and fecal microbiota transplantation—demonstrate preliminary benefits for gastrointestinal symptoms and selected behavioral outcomes, although clinical evidence remains heterogeneous and limited.
Conclusions: Current evidence supports a multifactorial model in which gut microbiota alterations act as modulatory amplifiers of neurodevelopmental vulnerability in ASD rather than as primary causal factors. Interactions among microbial metabolism, immune regulation, environmental exposures, and developmental timing appear central to this process. Future progress will depend on longitudinal, multi-omics approaches and biomarker-driven stratification to enable precision-based microbiota-targeted interventions.

KEYWORDS

Autism Spectrum Disorder, Gut–Brain Axis, Gut Microbiota, Immune Dysregulation, Microbial Metabolites, Therapeutic Interventions

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Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by persistent difficulties in social communication and social interaction, alongside restricted, repetitive patterns of behavior, interests, or activities [1,2]. The clinical manifestation of ASD spans a broad spectrum, encompassing wide variability in intellectual functioning, language development, adaptive behavior, and the presence of co-occurring medical and psychiatric conditions. Although advances in genetic and genomic research have identified numerous susceptibility genes and copy number variations associated with ASD, heritability estimates and molecular findings indicate that genetic factors alone are insufficient to explain the condition's marked phenotypic heterogeneity or rising prevalence [3]. These observations underscore the importance of complex interactions among genetic susceptibility, environmental exposures, and developmental timing in ASD pathophysiology.

Beyond its core behavioral features, ASD is increasingly recognized as a condition involving multisystem alterations. Individuals with ASD frequently exhibit gastrointestinal (GI) disturbances, metabolic abnormalities, immune dysregulation, and sleep disorders, suggesting that neurodevelopment may be influenced by dynamic interactions between central and peripheral biological systems [1,6]. This systemic perspective has prompted growing interest in integrative models that extend beyond the central nervous system (CNS) to include peripheral physiological processes capable of shaping brain development and function.

Among these models, the gut–brain axis has emerged as a critical bidirectional communication network linking the intestinal microbiota with the CNS through neural, immune, metabolic, and endocrine pathways [4,11]. The human gastrointestinal tract harbors a dense and metabolically active microbial ecosystem that contributes to nutrient metabolism, immune system maturation, epithelial barrier integrity, and the production of neuroactive compounds [5,15]. Rather than functioning as passive commensals, gut microbes act as a dynamic endocrine and immunological interface, generating bioactive metabolites, modulating cytokine signaling, and influencing neural activity. Communication along the gut–brain axis is mediated through vagal and enteric neural pathways, circulating immune mediators, microbial-derived metabolites, and hormonal signaling, enabling bidirectional influence between the gut and the brain [4,13,18].

Early life represents a particularly sensitive window for microbiota–brain interactions. Initial microbial colonization begins at birth and is shaped by delivery mode, breastfeeding, maternal microbiome composition, antibiotic exposure, and early dietary patterns [8]. These processes coincide with critical periods of immune programming and neurodevelopment, including synaptogenesis, myelination, and microglial maturation [19]. Microbial-derived signals are essential for the establishment of immune tolerance and balanced T cell differentiation [15], while peripheral immune cues and microbial metabolites influence the maturation and functional state of microglia within the CNS [19]. Disruptions to microbial composition or metabolic output during these developmental windows may therefore exert long-lasting effects on immune homeostasis, intestinal barrier function, and neural circuit refinement.

Clinical evidence further supports a link between gastrointestinal physiology and ASD. GI symptoms such as constipation, diarrhea, abdominal pain, and altered bowel habits are significantly more prevalent in individuals with ASD than in neurotypical populations [6,7]. In some cohorts, the severity of GI symptoms correlates with behavioral features including irritability, anxiety, and social impairment, although these associations do not establish causal relationships [6]. Consistent with these observations, microbiome studies have reported alterations in gut microbial diversity and composition in ASD, including reduced alpha diversity, enrichment of select *Clostridium* species, and decreased abundance of potentially beneficial taxa such as *Bifidobacterium* and *Faecalibacterium* [23–27]. Functional analyses suggest that microbial metabolic capacity, rather than taxonomic composition alone, may be particularly relevant, with reported disruptions in short-chain fatty acid (SCFA) production, lipopolysaccharide biosynthesis, and tryptophan metabolism [29,36].

SCFAs—including acetate, propionate, and butyrate—are generated through microbial fermentation of dietary fibers and play key roles in maintaining epithelial integrity, regulating immune responses, and modulating gene expression [36]. These metabolites can influence CNS function indirectly via immune and endocrine pathways and, under certain conditions, may affect microglial maturation, histone acetylation, and neurotransmitter systems [19,20]. Altered SCFA profiles have therefore been proposed as potential contributors to neuroimmune imbalance relevant to ASD. Similarly, microbial regulation of tryptophan metabolism affects serotonin synthesis and kynurenine pathway activity, processes implicated in both neurodevelopment and immune signaling [37,38]. Increased intestinal permeability and microbial endotoxin exposure may further promote systemic immune activation, linking gut dysbiosis to neuroinflammatory pathways [22].

Immune dysregulation represents another convergent feature of ASD pathophysiology. Elevated levels of pro-inflammatory cytokines, including interleukin-6, interleukin-17, tumor necrosis factor-α, and interferon-γ, have been reported in peripheral blood and, in some studies, within CNS tissue of individuals with ASD [32–35]. Alterations in T helper cell balance, including evidence of Th17 skewing, may compromise immune tolerance and sustain inflammatory signaling [34]. Microglial activation observed in postmortem analyses further supports persistent neuroimmune involvement in ASD [35]. Importantly, maternal immune activation models demonstrate that inflammatory perturbations during gestation can induce ASD-like phenotypes in offspring, highlighting the developmental sensitivity of neuroimmune pathways [16]. Many of these immune alterations intersect mechanistically with microbial signaling, positioning dysbiosis as a potential modulator rather than a primary etiological factor.

Current evidence does not support a reductionist model in which alterations of the gut microbiota independently cause ASD. Instead, ASD likely arises from complex interactions among genetic vulnerability, environmental influences, epigenetic regulation, and developmental timing [1,3]. Within this multifactorial framework, gut microbiota alterations may function as amplifiers of immune activation, metabolic signaling, and neural circuit modulation [4]. Microbiota-driven changes in cytokine profiles, metabolite availability, and barrier integrity may influence synaptic plasticity, excitatory–inhibitory balance, and network connectivity—processes central to ASD neurobiology.

Accordingly, therapeutic strategies targeting the gut microbiota—including probiotics, dietary interventions, and fecal microbiota transplantation—have been explored as potential approaches to alleviate gastrointestinal symptoms and modulate downstream immune and metabolic pathways in ASD [41,49,50]. While preliminary findings suggest improvements in GI symptoms and, in some cases, behavioral measures, heterogeneity in study design, sample size, and follow-up duration limits generalizability and causal inference.

In this review, we synthesize current evidence linking gut microbiota composition and function to immune dysregulation, metabolic signaling, and neurodevelopmental processes in ASD. We examine the physiological foundations of the gut–brain axis, characterize microbial and immune alterations associated with ASD, explore metabolite-mediated mechanisms influencing neural function, and evaluate emerging microbiota-targeted interventions. By integrating findings across microbiology, immunology, and neuroscience, we propose a systems-level framework in which the gut–brain axis represents a dynamic interface capable of modulating neurodevelopmental vulnerability in ASD, with implications for future biomarker development and stratified therapeutic strategies.

2. Physiology of the Gut–Brain Axis

The gut–brain axis is a bidirectional communication network integrating neural, immune, endocrine, and metabolic signaling between the gastrointestinal tract and the central nervous system (CNS). Through this system, intestinal microbial communities influence brain development and function, while central neural circuits regulate gastrointestinal motility, secretion, immune activity, and barrier integrity [4,11]. Understanding these physiological pathways provides a foundation for interpreting how microbial dysbiosis may modulate neurodevelopmental vulnerability in autism spectrum disorder (ASD).

2.1 Neural Pathways

Neural communication between the gut and brain is mediated primarily through the vagus nerve and the enteric nervous system. The vagus nerve constitutes the major afferent pathway transmitting sensory information related to luminal nutrients, microbial metabolites, and inflammatory mediators, while efferent vagal signaling regulates intestinal motility, secretion, and local immune responses [11,13].

Experimental studies demonstrate that microbial influences on behavior can depend on intact vagal signaling. In animal models, behavioral effects induced by specific probiotic strains are abolished following vagotomy, underscoring the vagus nerve as a key conduit for microbiota–brain communication [14]. These findings indicate that microbial signals can influence CNS function through rapid, neuronally mediated mechanisms.

In addition to vagal pathways, enteroendocrine cells within the intestinal epithelium act as sensory transducers that detect nutrients and microbial metabolites and release neuroactive molecules that stimulate afferent neurons in a synapse-like manner, enabling rapid gut-to-brain signaling [10].

2.2 Immune System Interactions

The gut microbiota plays a central role in immune maturation and maintenance of immune tolerance. Commensal microorganisms promote development of gut-associated lymphoid tissue and differentiation of regulatory T cells (Tregs), while balanced microbial communities regulate the equilibrium between pro-inflammatory T helper 17 (Th17) cells and anti-inflammatory Tregs [15].

Disruption of microbial–immune interactions can shift immune tone toward a pro-inflammatory state. In ASD, multiple studies report altered cytokine profiles and evidence of persistent low-grade inflammation, suggesting that immune dysregulation may intersect with neurodevelopmental processes [32–34].

Maternal immune activation (MIA) provides a mechanistic link between immune perturbation and altered neurodevelopment. Experimental models show that gestational inflammatory signaling disrupts fetal brain development, leading to long-lasting behavioral and neural circuit changes. These effects are mediated in part by microglia, which regulate synaptic pruning and circuit refinement and may disrupt excitatory–inhibitory balance when aberrantly activated during development [16,35].

2.3 Endocrine and Metabolic Signaling

Microbial metabolites function as systemic signaling molecules influencing host metabolism, immune regulation, and neural activity. Among these, short-chain fatty acids (SCFAs)—including acetate, propionate, and butyrate—are produced through bacterial fermentation of dietary fibers and exert broad physiological effects [18,36].

SCFAs regulate immune cell differentiation, enhance epithelial barrier integrity, and modulate gene expression through epigenetic mechanisms. Experimental evidence further indicates that SCFAs influence blood–brain barrier permeability and microglial maturation, providing a mechanistic bridge between gut microbial activity and CNS development [19,20,36].

Beyond SCFAs, gut microbes metabolize bile acids and dietary tryptophan into bioactive compounds that influence inflammatory regulation, neurotransmission, and epithelial integrity, extending microbial signaling beyond the gut to systemic and neural homeostasis [18,37].

2.4 Intestinal and Blood–Brain Barrier Integrity

The intestinal epithelium forms a selectively permeable barrier regulated by tight junction proteins sensitive to inflammatory signaling and microbial metabolites [22]. Dysbiosis and pro-inflammatory cytokines can disrupt barrier integrity, increasing intestinal permeability and facilitating systemic exposure to bacterial components such as lipopolysaccharide (LPS) [22,23].

Elevated circulating LPS activates innate immune receptors, promoting peripheral cytokine release and priming microglial activation within the CNS [24,33]. In parallel, the blood–brain barrier (BBB) regulates CNS exposure to peripheral immune and metabolic signals. Experimental evidence indicates that gut microbiota influence BBB permeability, particularly during development, suggesting a role in shaping CNS vulnerability to inflammatory and metabolic perturbations [20].

Altered intestinal and BBB integrity has been reported in subsets of individuals with ASD, supporting the hypothesis that barrier dysfunction may amplify immune and metabolic dysregulation within a multifactorial pathogenic framework [21,22].

3. Gut Microbiota Alterations in Autism Spectrum Disorder

Building upon the physiological framework of the gut–brain axis, numerous studies have examined whether individuals with autism spectrum disorder (ASD) exhibit distinct features of gut microbial composition and function. Although findings vary across cohorts and methodologies, convergent evidence indicates that subsets of individuals with ASD display alterations in microbial diversity, taxonomic composition, and metabolic capacity. These changes are heterogeneous and appear to reflect differences in clinical presentation, dietary patterns, and gastrointestinal comorbidities.

3.1 Reduced Microbial Diversity and Ecosystem Stability

Microbial diversity is commonly regarded as an indicator of ecosystem resilience and functional redundancy. Several studies report reduced alpha diversity in children with ASD compared with neurotypical controls, suggesting decreased microbial richness and evenness [23,24]. While not universally observed, differences in beta diversity—reflecting overall community composition—are more consistently reported, indicating distinct microbial community structures between ASD and control populations [23,27].

Reduced diversity may limit functional redundancy and increase vulnerability to perturbations such as antibiotic exposure, dietary restriction, or inflammatory stress [27]. In ASD, restrictive eating behaviors and selective food preferences may further constrain microbial diversity, positioning altered diversity as both a consequence of behavioral factors and a contributor to gastrointestinal and metabolic dysregulation.

3.2 Taxonomic Shifts Associated with ASD

Beyond diversity metrics, specific taxonomic shifts have been reported in ASD-associated microbiomes. Increased abundance of *Clostridium* species and related *Clostridiales* has been documented in several cohorts; these organisms are capable of producing neuroactive metabolites, including propionate [25,26]. Elevated levels of *Sutterella* species have also been observed, suggesting altered mucosal immune interactions [28,29].

Conversely, reduced abundance of taxa associated with anti-inflammatory activity and epithelial barrier support—such as *Bifidobacterium*, *Faecalibacterium*, and *Akkermansia*—has been reported across multiple studies [29,31]. As these organisms contribute to butyrate production and mucosal health, their depletion may compromise barrier integrity and immune regulation.

Importantly, no single microbial signature reliably distinguishes all individuals with ASD from neurotypical controls. Instead, observed patterns suggest multiple dysbiotic profiles influenced by diet, gastrointestinal symptom burden, medication exposure, and developmental history.

3.3 Functional and Metabolic Alterations of the ASD Microbiome

Functional metabolic capacity may be more relevant than taxonomic composition alone in shaping host–microbiome interactions. Metagenomic and metabolomic studies reveal alterations in microbial pathways related to lipopolysaccharide biosynthesis, oxidative stress, and amino acid metabolism in ASD-associated microbiomes [29,32].

Metabolomic analyses further demonstrate differences in circulating and fecal metabolites, including short-chain fatty acids and compounds involved in tryptophan metabolism [29,30]. Notably, altered metabolic profiles have been observed even in the absence of pronounced taxonomic differences, reinforcing the concept that microbial function and host–microbe interactions may be decoupled from compositional measures. This functional perspective aligns with emerging emphasis on mechanism over descriptive association in microbiome research [51].

3.4 Heterogeneity and Methodological Considerations

Despite growing evidence of microbiome alterations in ASD, substantial heterogeneity exists across studies. Variability in sequencing platforms, analytical pipelines, dietary control, age ranges, and clinical phenotyping complicates cross-study comparison and limits generalizability [32]. Moreover, many reported microbial differences may reflect secondary effects of restricted diets, gastrointestinal pathology, or medication use rather than primary contributors to ASD pathophysiology.

Accordingly, current evidence does not support a uniform “ASD microbiome” but instead suggests that dysbiosis characterizes specific subgroups within the spectrum. Integrating compositional, functional, immunologic, and clinical data will be essential for identifying biologically meaningful patterns and distinguishing causal mechanisms from correlational findings.

4. Immune Dysregulation and Neuroinflammation Associated with ASD

Accumulating evidence indicates that immune abnormalities represent a significant component of autism spectrum disorder (ASD) pathophysiology. Although immune dysregulation is not unique to ASD, convergent findings from peripheral, central, and developmental studies suggest that altered immune signaling may intersect with neurodevelopmental processes relevant to the disorder. Given the central role of the gut microbiota in immune maturation and regulation, microbial dysbiosis may amplify or sustain inflammatory responses that influence brain development and function.

4.1 Peripheral Immune Activation

Multiple studies have reported altered peripheral immune profiles in individuals with ASD, including elevated circulating levels of pro-inflammatory cytokines such as interleukin (IL)-6, IL-17, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) in plasma and serum [32–34]. Meta-analytic evidence further supports the presence of systemic immune activation in ASD, although effect sizes vary across cytokines and cohorts [33].

These cytokines are known to influence neurodevelopmental processes, including neuronal differentiation, synaptic plasticity, and network connectivity. IL-6, in particular, has been implicated in altered social behavior and excitatory–inhibitory imbalance in experimental models, highlighting a potential mechanistic link between peripheral immune activation and neural circuit dysfunction [16,33]. Similarly, IL-17 signaling has been associated with neurodevelopmental alterations in maternal immune activation models, suggesting developmental sensitivity to inflammatory cues [16].

Altered T cell phenotypes have also been described in ASD, including evidence of skewing toward T helper 17 (Th17) responses and impaired regulatory T cell (Treg) function [34]. Because gut microbiota play a critical role in shaping Th17 and Treg differentiation, dysbiosis may contribute to this imbalance, promoting a pro-inflammatory systemic environment. Such immune alterations may be further exacerbated by increased intestinal permeability, which permits translocation of microbial components such as lipopolysaccharide (LPS) into circulation [22,23].

Circulating LPS activates innate immune receptors, including toll-like receptor 4, triggering cytokine release and reinforcing inflammatory signaling [24]. This feed-forward loop may link gut barrier dysfunction, microbial dysbiosis, and sustained peripheral immune activation in subsets of individuals with ASD.

4.2 Neuroinflammation and Glial Cell Dysfunction

Evidence of neuroinflammation in ASD has been reported in postmortem brain tissue, characterized by activated microglia and astrocytes across multiple brain regions [35]. Microglia are the resident immune cells of the central nervous system and play essential roles in synaptic pruning, axonal guidance, and circuit refinement during development. Dysregulated microglial activation may therefore disrupt the balance between synapse formation and elimination, contributing to atypical connectivity patterns observed in ASD [35].

Activated microglia release pro-inflammatory cytokines and reactive oxygen species that can influence synaptic plasticity and neurotransmitter balance. Persistent activation may disturb excitatory–inhibitory equilibrium, a core neurobiological feature implicated in ASD [16,35]. Astrocytes, which regulate synaptic support, neurotransmitter uptake, and metabolic coupling, also exhibit altered activation states in neuroinflammatory contexts, potentially compounding neuronal network instability.

Importantly, microglial maturation and functional responsiveness are shaped by microbial-derived signals. Experimental studies demonstrate that gut microbiota and their metabolites, particularly short-chain fatty acids, are required for normal microglial development and immune competence [19]. In the absence of appropriate microbial signaling, microglia exhibit immature phenotypes and altered inflammatory responses. These findings provide a mechanistic basis for indirect microbial modulation of neuroimmune processes relevant to ASD.

4.3 Developmental Immune Perturbations and Maternal Immune Activation

Developmental timing is a critical determinant of immune effects on neurodevelopment. Maternal immune activation (MIA) models provide compelling evidence that inflammatory perturbations during gestation can alter fetal brain development and induce long-lasting behavioral and neurobiological changes in offspring [16]. In these models, maternal exposure to immune challenges elevates cytokines such as IL-6 and IL-17, which can cross the placenta and influence fetal neurodevelopment.

MIA-induced alterations include disrupted cortical organization, changes in synaptic connectivity, and ASD-like behavioral phenotypes in offspring [16]. Microglia are central mediators of these effects, responding to inflammatory cues during critical periods of brain development. Because maternal gut microbiota influence systemic immune tone and cytokine production, alterations in maternal microbial composition may modulate the severity and nature of MIA-related neurodevelopmental outcomes [15,16].

Collectively, these findings suggest that immune dysregulation in ASD reflects a convergence of peripheral immune activation, neuroinflammatory processes, and developmental immune perturbations. Rather than acting as a primary etiological factor, immune dysfunction may interact with genetic susceptibility and microbial signaling to shape neurodevelopmental trajectories.

5. Microbial Metabolites and Neurotransmission

Beyond immune-mediated mechanisms, gut microbiota influence neurodevelopment and behavior through the production of bioactive metabolites that modulate gene expression, neurotransmitter systems, mitochondrial function, and barrier integrity. Increasing evidence suggests that alterations in microbial metabolic output, rather than microbial composition alone, represent a key interface linking gut microbiota to neurodevelopmental processes relevant to autism spectrum disorder (ASD).

5.1 Short-Chain Fatty Acids (SCFAs)

Short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, are among the most extensively studied microbial metabolites within the gut–brain axis [18,36]. Generated through bacterial fermentation of dietary fibers, SCFAs exert systemic effects via immune, endocrine, and epigenetic pathways.

Butyrate acts as a histone deacetylase inhibitor, regulating gene expression in immune cells and neurons, while SCFAs more broadly enhance intestinal epithelial integrity and influence blood–brain barrier permeability, thereby modulating central nervous system (CNS) exposure to peripheral signals [18,20–22]. SCFAs are also required for appropriate microglial maturation and immune responsiveness, linking microbial metabolism to neuroimmune regulation [19].

Physiological concentrations of SCFAs support immune tolerance and neural homeostasis; however, excessive exposure to specific SCFAs, particularly propionate, has been shown in animal models to induce repetitive behaviors, social impairments, mitochondrial dysfunction, and neuroinflammatory changes reminiscent of ASD-related phenotypes [31,38]. These findings highlight the importance of tightly regulated microbial metabolic balance.

5.2 Tryptophan Metabolism and Indole Derivatives

Tryptophan metabolism represents another critical pathway through which gut microbes influence neurobiology. Intestinal bacteria convert dietary tryptophan into serotonin precursors, kynurenine pathway intermediates, and indole derivatives that modulate mood regulation, immune tolerance, and synaptic function [37,40].

Alterations in tryptophan metabolism have been reported in ASD, including imbalances in serotonin and kynurenine pathway activity [38,40]. Kynurenine metabolites influence glutamatergic neurotransmission and immune signaling, while indole derivatives interact with host receptors involved in epithelial integrity and inflammatory regulation and may influence astrocyte and microglial function [37]. Although causal relationships remain to be fully established, dysregulated tryptophan metabolism represents a plausible link between microbial activity, immune signaling, and neurotransmitter imbalance in ASD.

5.3 GABA, Glutamate, and Excitatory–Inhibitory Balance

Excitatory–inhibitory (E/I) imbalance is a central neurobiological hypothesis in ASD, reflecting altered balance between glutamatergic excitation and gamma-aminobutyric acid (GABA)-mediated inhibition within neural circuits [40,43]. GABA serves as the principal inhibitory neurotransmitter in the CNS and is essential for regulating synaptic plasticity and network stability.

Certain gut microbes, including species within the *Lactobacillus* and *Bifidobacterium* genera, are capable of synthesizing GABA from glutamate [39]. Although peripheral GABA does not freely cross the blood–brain barrier, microbial-derived GABA and related metabolites may influence CNS function indirectly and context-dependently through vagal signaling and modulation of enteric and immune pathways [14,39]. Disruption of GABAergic signaling has been consistently implicated in ASD, supporting the plausibility of microbiota-mediated modulation of E/I balance [40,43].

5.4 Additional Neuroactive Metabolites

Microbial metabolism also generates bile acids, polyamines, and monoamine-related compounds with neuroactive and immunomodulatory properties. Gut microbes convert primary bile acids into secondary bile acids that interact with host nuclear receptors involved in metabolic and inflammatory regulation [18,22]. Dysbiosis may alter bile acid profiles, potentially favoring pro-inflammatory signaling.

Polyamines such as spermidine and putrescine regulate cellular proliferation, autophagy, and synaptic plasticity, and altered polyamine metabolism has been reported in ASD-related metabolomic studies [30,40]. In addition, certain microbial species influence the availability of dopamine- and serotonin-related compounds, which may affect anxiety, mood regulation, and repetitive behaviors [40].

Collectively, microbial metabolites act across immune, metabolic, epigenetic, and synaptic domains, forming an interconnected network capable of shaping neurodevelopmental trajectories. These effects occur within a broader multifactorial context involving host genetics, immune status, and environmental exposures.

6. Early-Life Microbiota and Neurodevelopment

Neurodevelopment is highly sensitive to biological and environmental inputs during defined critical windows. The establishment of the gut microbiota occurs in parallel with rapid brain growth, synaptogenesis, immune maturation, and neural circuit refinement. Perturbations to microbial colonization and immune signaling during these early-life periods may therefore exert lasting effects on neurodevelopmental trajectories relevant to autism spectrum disorder (ASD).

6.1 Microbial Colonization and Critical Developmental Windows

Initial microbial colonization begins at birth and evolves dynamically throughout infancy. Delivery mode, breastfeeding, maternal microbiome composition, antibiotic exposure, and early nutrition play central roles in shaping microbial community assembly [5,8]. Vaginal delivery typically promotes early colonization

with maternal microbes, whereas cesarean section is associated with delayed colonization and reduced microbial diversity [8].

These colonization processes coincide with critical periods of immune and neural development. Early microbial exposure promotes maturation of gut-associated lymphoid tissue, expansion of regulatory T cells, and establishment of immune tolerance [13,15], while the developing brain undergoes synaptogenesis and circuit refinement dependent on appropriate microglial maturation and immune signaling [19].

Experimental evidence highlights the importance of timing in microbiota–brain interactions. Germ-free animal models exhibit altered synaptic protein expression, exaggerated stress responses, and social behavior deficits, many of which can be partially normalized by microbial colonization during early life but not adulthood [19]. Disruption of microbial assembly during these sensitive periods—through antibiotics, dietary restriction, or inflammatory stress—may therefore alter immune programming, barrier integrity, and microbial metabolite production. Given the frequent occurrence of early-life gastrointestinal disturbances and feeding selectivity in children later diagnosed with ASD, such perturbations may contribute to atypical neurodevelopmental outcomes [6,7].

6.2 Maternal Microbiome and Prenatal Immune Influences

The maternal immune and microbial environment during pregnancy represents an additional determinant of offspring neurodevelopment. Maternal immune activation (MIA) models demonstrate that gestational inflammatory perturbations can disrupt fetal brain development and induce long-lasting behavioral and neurobiological changes in offspring [16]. Elevated maternal cytokines, including interleukin-6 and interleukin-17, can cross the placenta and influence fetal neurodevelopmental processes.

The maternal gut microbiota regulates systemic immune tone and cytokine production during pregnancy. Alterations in maternal microbial composition may therefore modulate gestational inflammation and shape fetal neurodevelopment through immune-mediated pathways [15,16]. Microbial metabolites such as short-chain fatty acids can also reach the fetal compartment and influence immune development and epigenetic programming [18,20]. While physiological exposure supports normal development, imbalanced signaling during critical periods may alter neural circuit formation and long-term neuroimmune regulation.

Together, early microbial colonization and maternal immune–microbiota interactions act as developmental modulators that interact with genetic susceptibility and postnatal environmental exposures to influence neurodevelopmental trajectories rather than serving as deterministic causes of ASD.

7. Environmental Modulators of the Gut–Brain Axis

Environmental exposures shape the gut microbiota across the lifespan and may interact with genetic susceptibility and immune regulation to influence gut–brain axis function in ASD. These factors can amplify or attenuate microbial dysbiosis and immune activation, thereby modulating neurodevelopmental outcomes.

7.1 Antibiotic Exposure

Antibiotics exert profound effects on microbial diversity and community stability. Experimental and clinical studies demonstrate that antibiotic exposure reduces microbial richness, disrupts short-chain fatty acid production, and alters intestinal barrier integrity [27]. When such disruptions occur during early life, they may have prolonged consequences for immune programming and metabolic regulation.

Animal models show that antibiotic-induced microbial depletion is associated with altered social behavior, stress reactivity, and neurochemical profiles, effects that can be partially reversed through microbial reconstitution [19]. Although causal relationships in humans remain complex, these findings suggest that early or repeated antibiotic exposure may represent a modifiable environmental factor influencing microbiota–brain communication during sensitive developmental windows.

7.2 Diet and Microbial Metabolism

Diet is a major determinant of gut microbial composition and metabolic output. Diets rich in fermentable fiber promote short-chain fatty acid–producing bacteria, whereas low-fiber, highly processed diets are associated with reduced microbial diversity and diminished butyrate production [18,36]. These effects are particularly relevant in ASD, where selective eating behaviors are common [6].

Selective feeding patterns may contribute to both nutritional imbalance and microbial dysbiosis, reinforcing gastrointestinal symptoms and immune dysregulation. Conversely, dietary diversification and increased fiber intake may enhance microbial metabolic capacity and support epithelial barrier integrity [18,36]. In addition, dietary polyphenols and other bioactive compounds interact with gut microbes to influence anti-inflammatory signaling and metabolite production, further shaping gut–brain axis dynamics [18].

7.3 Environmental Stressors and Inflammatory Exposures

Environmental stressors, including physiological stress and inflammatory exposures, may further influence gut–brain axis function by altering microbial composition, compromising epithelial barrier integrity, and promoting systemic immune activation [22,24]. In susceptible individuals, these effects may act synergistically with dysbiosis to amplify neuroimmune signaling.

Collectively, antibiotic exposure, dietary patterns, and environmental stressors function as modulators of microbial ecology and gut–brain communication. Their effects depend on timing, intensity, and interaction with host biology, reinforcing the need for integrative models that consider environmental context alongside genetic and developmental factors.

8. Microbiota-Targeted Therapeutic Interventions in Autism Spectrum Disorder

Growing recognition of gut–brain axis involvement in autism spectrum disorder (ASD) has stimulated interest in microbiota-targeted interventions as adjunctive therapeutic strategies. While current evidence does not support microbiota modulation as a primary treatment for core ASD features, emerging data suggest potential benefits for gastrointestinal symptoms, immune regulation, and selected behavioral outcomes in specific subgroups. Therapeutic approaches explored to date include probiotics and prebiotics, dietary interventions, and fecal microbiota transplantation (FMT), although substantial heterogeneity across studies necessitates cautious interpretation.

8.1 Probiotics and Prebiotics

Probiotics—live microorganisms conferring health benefits when administered in adequate amounts—have been evaluated in several ASD cohorts. Commonly studied strains include *Lactobacillus* and *Bifidobacterium* species, which support epithelial barrier integrity, regulatory T cell induction, and microbial metabolite production [13,39].

Clinical studies and meta-analyses report improvements in gastrointestinal symptoms following probiotic supplementation in some individuals with ASD, with inconsistent evidence for modest behavioral benefits influenced by strain selection, dosage, and treatment duration [41,43]. Prebiotics, which promote the growth of beneficial microbial taxa, enhance short-chain fatty acid production and mucosal barrier function [18,36]. Given the reduced abundance of SCFA-producing bacteria reported in subsets of individuals with ASD [29,31], prebiotic supplementation may help restore microbial metabolic balance, although controlled evidence remains limited.

8.2 Dietary Interventions

Dietary modification is widely adopted in ASD management and includes gluten-free and casein-free diets, elimination diets, ketogenic diets, and increased fiber intake. Systematic reviews indicate mixed evidence for improvement in core ASD symptoms, though some individuals experience reductions in gastrointestinal discomfort and improved overall well-being [46,47].

Diet directly shapes microbial composition and metabolic output. Increased intake of fermentable fibers promotes SCFA production and epithelial barrier integrity, whereas low-fiber, highly processed diets may reduce microbial diversity and exacerbate dysbiosis [18,36]. Dietary patterns such as Mediterranean-style diets have been associated with favorable microbial and anti-inflammatory metabolic profiles in non-ASD populations, suggesting potential relevance for microbiota modulation [48]. Given the prevalence of selective eating behaviors in ASD, dietary interventions should be individualized and monitored to avoid nutritional compromise [6].

8.3 Fecal Microbiota Transplantation and Microbiota Transfer Therapy

FMT involves the transfer of processed stool from a healthy donor to restore microbial diversity and ecosystem stability. Although established for recurrent *Clostridioides difficile* infection, FMT has been explored experimentally in ASD populations.

Open-label studies report sustained improvements in gastrointestinal symptoms and long-term alterations in microbial composition following microbiota transfer therapy in children with ASD, with some studies also describing behavioral improvements [9,49]. Proposed mechanisms include restoration of SCFA-producing taxa, reduction of endotoxin-producing bacteria, enhancement of epithelial barrier integrity, and attenuation of systemic inflammation [18,22]. However, FMT remains experimental in ASD, with unresolved questions regarding long-term safety, durability of engraftment, donor selection, and regulatory oversight [50].

8.4 Translational Challenges and Toward Stratified Therapies

Despite biological plausibility, several challenges limit clinical translation of microbiota-targeted interventions. ASD heterogeneity suggests that uniform responses are unlikely [1,3], and many reported microbial alterations may reflect secondary effects of diet, medication exposure, or gastrointestinal pathology rather than primary drivers of neurodevelopmental change [23–27]. Methodological variability across studies further complicates reproducibility and interpretation [32,51].

Future therapeutic strategies may benefit from stratification based on microbial, immunologic, or metabolic biomarkers. Combination approaches integrating dietary modification, probiotic or prebiotic supplementation, and established behavioral and educational therapies may yield synergistic benefits. As mechanistic understanding advances, integration of multi-omics profiling with longitudinal clinical trials may support development of personalized microbiota-based interventions tailored to individual biological signatures [22,31,32,52].

9. Discussion

This review integrates evidence across microbiology, immunology, neuroscience, and clinical research to examine the role of the gut–brain axis in autism spectrum disorder (ASD). Current findings support a complex, dynamic system in which gut microbiota, immune signaling, metabolic outputs, and neural development interact across critical developmental windows. Within this framework, alterations of the gut microbiome are best understood as modulatory factors that can amplify or attenuate neurodevelopmental vulnerability in genetically and environmentally susceptible individuals, rather than as primary causes of ASD.

9.1 From Association to Mechanistic Convergence

A central challenge in ASD microbiome research is distinguishing association from mechanism. Although numerous studies report altered microbial composition, reduced diversity, and metabolic changes in subsets of individuals with ASD [23–31], heterogeneity across cohorts and methodologies precludes identification of a single, consistent "ASD microbiome." Functional and metabolomic analyses instead suggest that microbial metabolic output—rather than taxonomic composition alone—may exert more direct influence on host immune and neural pathways [29,30,32].

Converging evidence identifies shared mechanistic nodes linking microbial signaling to neurodevelopment, including immune regulation, epithelial and blood–brain barrier integrity, and neurotransmitter balance [18–22,36–40]. These intersecting pathways provide biological plausibility for gut–brain interactions in ASD while underscoring their context dependence and sensitivity to developmental timing, host genetics, and environmental exposures.

9.2 Immune Modulation as a Central Interface

Immune dysregulation emerges as a key interface linking microbial alterations to neurodevelopmental processes in ASD. Peripheral immune activation, altered cytokine profiles, and neuroinflammatory changes have been reported across multiple studies [32–35], and experimental models demonstrate that immune perturbations during sensitive developmental periods can induce long-lasting changes in neural circuitry and behavior [16].

Gut microbiota shape immune maturation, T cell balance, and inflammatory tone [13,15]. Dysbiosis, increased intestinal permeability, and altered microbial metabolite production may therefore amplify immune signaling cascades that influence microglial function and synaptic refinement [19,22,35]. These immune alterations act in concert with microbial and metabolic factors rather than in isolation.

9.3 Developmental Timing and Environmental Context

Developmental timing is a recurring theme across gut–brain axis research. Early-life microbial colonization coincides with periods of rapid brain development and immune programming, creating windows of heightened sensitivity to perturbation [8,19]. Evidence from germ-free and maternal immune activation models highlights the importance of microbial and immune signals during these periods [16,19].

Environmental modulators—including antibiotic exposure, diet, and inflammatory stressors—further shape microbial ecology and immune signaling across development [18,19,27]. In ASD, selective eating behaviors and gastrointestinal comorbidities may reinforce dysbiosis and complicate causal interpretation [6]. Together, these findings support a model in which environmental exposures interact dynamically with microbiota and host biology, contributing to clinical heterogeneity.

9.4 Therapeutic Implications and Translational Limits

Microbiota-targeted interventions remain a promising but exploratory area of ASD research. Probiotics, dietary strategies, and fecal microbiota transplantation have shown potential benefits for gastrointestinal symptoms and, in some cases, behavioral measures [9,41,46–49]. However, variability in study design, small sample sizes, and limited placebo-controlled trials constrain generalizability.

Given ASD heterogeneity, microbiota-based interventions are unlikely to be universally effective [1,3]. Stratification based on microbial, immunologic, or metabolic profiles may be necessary to identify individuals most likely to benefit [22,31]. Importantly, microbiota modulation should be considered an adjunctive strategy aimed at improving systemic homeostasis rather than a replacement for established behavioral, educational, and medical interventions.

9.5 Methodological Considerations and Future Directions

Methodological variability—including differences in sequencing platforms, bioinformatic pipelines, dietary control, and outcome measures—continues to limit reproducibility and cross-study comparison [32]. Longitudinal, multi-omics approaches integrating metagenomics, metabolomics, immunophenotyping, and clinical phenotyping will be essential for clarifying temporal relationships and identifying causal mechanisms [51].

Future research should prioritize mechanistic studies linking microbial metabolites to specific neuroimmune pathways and well-powered clinical trials incorporating biomarker-based stratification. Advances in precision microbiome engineering and systems biology may ultimately enable targeted modulation of gut–brain signaling pathways relevant to ASD [52]. Within this framework, gut microbiota alterations function as modulatory amplifiers rather than primary determinants of ASD pathophysiology.

Conclusions

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by substantial clinical, biological, and etiological heterogeneity. Growing evidence indicates that the gut–brain axis represents an important modulatory system through which microbial, immune, metabolic, and neural processes interact across development. Rather than supporting a singular causal role for the gut microbiota, current findings point to a multifactorial model in which microbial alterations influence neurodevelopmental vulnerability by interacting with genetic susceptibility, immune regulation, environmental exposures, and developmental timing.

This review highlights several convergent mechanisms linking gut microbiota to ASD-related biology, including immune dysregulation, altered microbial metabolite production, barrier dysfunction, and modulation of neurotransmitter systems. Immune signaling and neuroinflammation emerge as central interfaces through which microbial and metabolic factors may influence neural circuit development, particularly during sensitive prenatal and early postnatal periods. Environmental modulators such as diet, antibiotic exposure, and inflammatory stress further shape microbial ecology and gut–brain communication, contributing to interindividual variability within the autism spectrum.

Therapeutic strategies targeting the gut microbiota—including probiotics, dietary interventions, and fecal microbiota transplantation—show preliminary promise in alleviating gastrointestinal symptoms and modulating systemic physiology in selected individuals with ASD. However, evidence remains heterogeneous, and microbiota-based interventions should currently be regarded as adjunctive approaches rather than primary treatments for core ASD features. Careful consideration of safety, long-term efficacy, and individual biological context is essential.

Future progress in this field will depend on integrative, longitudinal research designs that combine microbiome profiling with metabolomic, immunologic, and neurodevelopmental measures. Biomarker-driven stratification and systems-level approaches may enable identification of subgroups most likely to benefit from targeted interventions. As mechanistic understanding deepens, the gut–brain axis may provide a valuable framework for developing precision-based strategies aimed at improving systemic homeostasis and quality of life in individuals with ASD.

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