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THE MICROBIOTA-GUT-BRAIN AXIS IN NEUROLOGICAL DISEASE-A REVIEW

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ABSTRACT:

The microbiota–gut–brain axis is a bidirectional communication network connecting the intestinal tract, the enteric nervous system, and the central nervous system through neural, endocrine, immune, and metabolic pathways. Converging evidence implicates gut dysbiosis in the onset and progression of autism spectrum disorder (ASD), Parkinson’s disease (PD), and Alzheimer’s disease (AD). This research-style review synthesizes mechanistic insights on barrier dysfunction, neuroinflammation, microbial metabolites, and neuromodulators that bridge intestinal ecology with brain structure and function. Particular emphasis is placed on organism-level microbial signatures and clinically tractable biomarkers, including fecal calprotectin, short-chain fatty acids (SCFAs), hydrogen sulfide, sulfite, lipopolysaccharide (LPS), trimethylamine N-oxide (TMAO), tryptophan–kynurenine intermediates, glial markers (GFAP, Sox-10), and alpha-synuclein (α -syn) species. We integrate dietary and microbial therapeutics—vegetarian, Mediterranean, low-protein high-carbohydrate, ketogenic, probiotic, prebiotic, synbiotic, antibiotic, and fecal microbiota transplantation—linking them to distinct microbial shifts such as increases in *Akkermansia muciniphila*, *Bifidobacterium*, and *Lactobacillus*, and decreases in SCFA-producers including *Lachnospiraceae*, *Roseburia*, *Faecalibacterium*, *Blautia*, *Coprococcus*, and *Butyrivibrio* observed across disorders. Together, these data support a testable model in which intestinal dysbiosis and barrier failure trigger inflammatory and neuroendocrine cascades that exacerbate proteinopathy, synaptic failure, and circuit-level dysfunction. The review concludes with future directions for personalized diagnostics and nutrition-based interventions.

Introduction

The human gastrointestinal tract harbors an immense microbial ecosystem comprising roughly one thousand species and several thousand strains that together establish a dynamic metabolic and immunological organ. Far from merely digesting nutrients, the gut microbiota signal to the brain via the

vagus nerve, circulating cytokines, hormones, and microbially derived metabolites. This bidirectional interface—often termed the microbiota–gut–brain axis—links emotional and cognitive processes to intestinal motility, permeability, and immune tone. Dysbiosis, the disruption of microbial composition and function, is increasingly recognized as a driver of neuro-



developmental and neurodegenerative disorders, including ASD, PD, and AD. Patients frequently exhibit gastrointestinal complaints years before overt neurological symptoms, and neuropathology can be detected in the enteric nervous system (ENS) prior to central lesions. Together these observations motivate a systems view in which gut homeostasis is a determinant of brain resilience.

Two structural barriers integrate this system: the intestinal epithelial barrier and the blood–brain barrier (BBB). A compromised intestinal barrier (“leaky gut”) permits microbe-associated molecular patterns and metabolites to enter the portal and systemic circulation. If the BBB is also permeable, these circulating signals reach the brain, activating microglia and astrocytes, amplifying neuroinflammation, and promoting protein misfolding cascades. Glucocorticoids released by the hypothalamic–pituitary–adrenal (HPA) axis connect psychosocial stress to mucosal immunity and neural function, while enteroendocrine hormones such as GLP-1, peptide YY, and ghrelin provide an endocrine channel back to the brain. This framework is supported by observations that stress dysregulates the HPA axis, increases cortisol, and correlates with cognitive decline and heightened AD risk, whereas appropriate glucocorticoid signaling is essential for neurodevelopment and memory.

The Microbiota–Gut–Brain Axis: Anatomy and Signaling

Communication across the axis occurs along several routes. The neural route is exemplified by vagal afferents that sense luminal activity indirectly through enteroendocrine and immune cells. The endocrine route involves gut hormones and adrenal glucocorticoids, while the immune route is mediated by cytokines, chemokines, and

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pattern-recognition receptor pathways such as TLR2 and TLR4. The metabolic route consists of microbial products including SCFAs (acetate, propionate, butyrate), indole derivatives from tryptophan, secondary bile acids, polyamines, TMAO, and gaseous mediators such as hydrogen sulfide. The metabolites binds to GPCR, blocks histone deacetylases, alter mitochondrial respiration, which directly leads to synaptic plasticity.

Barrier Integrity and Bidirectional Permeability

Molecules present in the intestinal lumen traverse the epithelium by paracellular and transcellular routes. Tight junction proteins regulate paracellular flux, when the tight junction is disrupted by inflammation or dysbiosis, it leads to increase in permeability, which allow lipopolysaccharide from Gram-negative bacteria, bacterial amyloids such as curli, and sulfide species to access the lamina propria and bloodstream. A leaky BBB intensify the problem by admitting proinflammatory cytokines and microbial products into the brain parenchyma. Microglial and astrocytic activation under these conditions drives neuroinflammation, oxidative stress, and neuronal death, as observed in PD and AD. Fecal and plasma biomarkers of barrier breach—including calprotectin, LPS-binding activity, and

circulating TMAO—mirror these processes and are increasingly used to profile patients.

Gut Microbiota in Brain Development and Function

Early-life colonization establishes immune tolerance and calibrates endocrine and neural circuits. Disruption during this sensitive window alters microglial maturation, serotonergic signaling, and stress reactivity. Germ-free and antibiotic-perturbed models



show abnormal social behavior and cognitive deficits that can be rescued by microbiota reconstitution. Human data indicate that mode of delivery, breastfeeding, maternal diet, obesity, and inflammation reshape infant microbiomes in ways that track later neurobehavioral outcomes.

Parkinson's Disease

Parkinson's disease is a progressive movement disorder defined by degeneration of dopaminergic neurons in the substantia nigra and the accumulation of misfolded α -synuclein. Pathologic changes in the ENS occur early, even before central lesions. Atrophic degeneration of myenteric and submucosal neurons accompanied by colocalized α -syn deposits has been described, dovetailing with the long prodrome of constipation and hypo-motility. Clinically, patients experience tremor, rigidity, bradykinesia, postural instability, and a constellation of non-motor features including REM sleep behavior disorder, hyposmia, anxiety, depression, and gastrointestinal dysfunction. Enteral problems such as malnutrition, *Helicobacter pylori* infection, and marked constipation are common, and constipation symptoms may arise from vasoactive intestinal peptide secretomotor neuron dysfunction in the submucosal plexus.

Dysbiosis in PD is robust. Alpha diversity can be increased yet skewed, whereas beta diversity demonstrates clear separation from healthy controls. Microbial signatures include reduced SCFA-producing taxa from the Lachnospiraceae family and genera such as *Blautia*, *Coprococcus*, *Butyrivibrio*, *Roseburia*, *Faecalibacterium*, *Fusicatenibacter*, and *Prevotella*, alongside increases in LPS-rich and proinflammatory groups including *Enterobacteriaceae*, *Bacteroides*, *Oscillospira*, *Ralstonia*, and specific opportunists. Several studies report that differential abundance of microbes like

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Holdemania, *Anaerotruncus*, *Clostridium* clusters IV and XVIII, *Sphingomonas*, *Aquabacterium*, and *Butyricicoccus*. *Akkermansia muciniphila* and *Bilophila wadsworthia* often increases and correlate with symptom intensity; the above species influence mucus integrity and sulfur metabolism, with *A. muciniphila* involve in hydrogen sulfide production and *Bilophila* serves as a pivotal sulfite-generating organism.

Biomarkers in PD concentrate on barrier disruption and inflammatory tone. Decreased abundance of SCFA producing organism integrates with reduced fecal butyrate, higher fecal calprotectin, and impaired epithelial integrity. Calprotectin indicates low-grade intestinal inflammation; its elevation in PD resembles reduced butyrate producers and clinical severity. Sulfite and hydrogen sulfide represent as a key microbial toxins. Certain *Desulfovibrio* species proliferate in PD stools, synthesize LPS and magnetite nanoparticles, generate high levels of H_2S that overwhelm mucosal detoxification, and may accelerate α -syn aggregation and transport of toxic species across the BBB. Elevated glial markers such as GFAP and Sox-10 in PD gastrointestinal tissue signify enteric gliosis and are associated with proinflammatory cytokines.

Alzheimer's Disease

Alzheimer's disease (AD) is characterized pathologically defined as extracellular amyloid- β ($A\beta$) plaques and intracellular neurofibrillary tangles formed by hyperphosphorylated tau, with synaptic failure and progressive cognitive decline. Amyloidogenic processing of amyloid precursor protein (APP) by BACE1 and γ -secretase produces $A\beta_{40}$ and $A\beta_{42}$. $A\beta_{42}$ leads to oligomerization into protofibrils and fibrils that develop plaques, while tau undergoes



phosphorylation, acetylation, and truncation that inhibits microtubule binding and promote aggregation. Elevated TNF- α , IL-1 β , and other inflammatory mediators are consistently found in AD and act both as cause and consequence of pathology.

Microbiota alterations in AD include reduced Firmicutes and SCFA producers such as *Ruminococcus* and Clostridiaceae, decreased *Eubacterium rectale* and *Bacteroides fragilis*, and increased proinflammatory Proteobacteria including Gammaproteobacteria, Enterobacteriales, and Enterobacteriaceae. *Escherichia/Shigella* often increase, and their endotoxin LPS has been detected in high amounts within neocortical and hippocampal tissue. Bacterial amyloids, notably curli from *E. coli*, share structural features with human pathological amyloids and cross-seed A β and α -syn aggregation, intensifying neuroinflammation via TLR2 and TLR4 signaling.

Biomarkers in AD extend from microbial products to host responses. Circulating and cerebrospinal fluid TMAO is elevated in cognitively impaired patients and crosses the BBB.

Direct interactions between pathogens and amyloid biology have been reported. Persistent *Helicobacter pylori* infection elicits cytokines and amyloids and is associated with worse cognition, while eradication therapy has improved cognitive measures in small studies. *Chlamydia pneumoniae* invasion of astrocytes stimulates A β production. Microbial amyloids beyond curli—including phenol-soluble modulins from *Staphylococcus aureus*, TasA from *Bacillus subtilis*, chaplins from *Streptomyces coelicolor*, FapC from *Pseudomonas fluorescens*, and MccE492 from *Klebsiella pneumoniae*—provide numerous cross-seeding candidates within a dysbiotic gut.

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Dietary changes interferes with the biomarkers. Mediterranean patterns that rich in polyphenols, fibers, and marine PUFAs correlate with lower AD incidence and slow disease progression by increasing *Lactobacillus*, *Bifidobacterium*, *Akkermansia muciniphila*, and SCFA producers, suppress the pathobionts. Ketogenic strategies turns ketone bodies as alternative neural fuel in case of impaired glucose utilization, improve the vascular and metabolic profiles, and also increases beneficial taxa with reducing *Desulfovibrio* and *Turicibacter*. Probiotic formulations with *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, and *Bifidobacterium lactis* have reduced excess A β levels and improved cognition in clinical and pre-clinical settings, often with increased serum and brain SCFAs and lactate.

Autism Spectrum Disorder

Autism spectrum disorder (ASD) encompasses a heterogeneous group of neurodevelopmental conditions marked by impairments in social communication and restricted, repetitive behaviors. Gastrointestinal complaints are frequent and correlate with behavioral severity. Increased intestinal permeability leads to exposure of the immune system with luminal antigens and toxins, produces systemic responses that improves neural development and function.

Dysbiosis patterns in ASD includes reduced counts of *Prevotella*, *Coprococcus*, and members of the Veillonellaceae, with lower *Enterococcus*, *Escherichia coli*, *Bifidobacterium*, and *Bacteroides* in some cohorts, also reveals higher *Faecalibacterium*, *Lactobacillus*, and *Ruminococcus*. Elevated levels of *Clostridium histolyticum*, recognized toxin producers has been documented. vancomycin was administered to



reduce the clostridia in improved ASD features, involved their metabolites in symptom generation.

Relationship between Maternal microbiome and immunity bridge in early-life risk. In maternal immune activation models, Th17 cells and IL-17A are increased, if maternal IL-17A acts on fetal IL-17 receptors causes cortical malformations and ASD-like behaviors. Treatment with the human commensal *Bacteroides fragilis*, with corrected microbial composition, improved barrier function, and normalized behaviors, improves the causal role of gut ecology. Metabolomic changes in ASD feces include elevated levels of SCFAs such as acetate, propionate, butyrate, and branched-chain acids, higher isopropanol, and lower GABA, each SCFAs are capable of affecting neuronal excitability and microglial tone.

Environmental and perinatal factors contribute their activity in reducing the risk through the microbiome. Maternal obesity associates with increased features of ASD, and high-fat diet induces offspring dysbiosis and social deficits that are prone to transmit through microbiota transfer. Mode of delivery includes breastfeeding initiation and duration early antibiotic exposure causes isolation culture and, neurodevelopmental passages. Prolonged breastfeeding interacts with reduced ASD incidence and develops fewer gastrointestinal symptoms by promoting *Bifidobacterium* and *Lactobacillus* and suppressing pathobionts.

Therapeutic approaches control these mechanisms. Probiotics containing *Lactobacillus* and *Bifidobacterium* reduce gastrointestinal symptoms and may improve behavior. Gluten- and casein-restricted diets serve as benefit in some children by reduc-

ing proinflammatory peptides. Fecal microbiota transplantation has produced visible improvements in small trials, by supporting a role for comprehensive microbial remodeling. Precision nutrition that increases fibers, polyphenols, and omega-3 PUFAs known to normalize metabolite profiles and supports synaptic plasticity.

Cross-Cutting Biomarkers and Mechanistic Convergence

Across ASD, PD, and AD, several biomarker classes repeatedly emerge. SCFAs tend to reflect fermentative capacity, butyrate tends to modulate histone acetylation, also improves colonocytes and promotes tight-junction integrity. It may exacerbate microgliosis under specific pathological conditions. Calprotectin tends to reflect mucosal neutrophil activation and also rises with some loss of SCFA producers. Sulfite and hydrogen sulfide constitutes sulfur metabolism and interfere with mucus integrity. Increased availability of *Bilophila wadsworthia*, *Akkermansia muciniphila*, and *Desulfovibrio* contributes to barrier failure. LPS highlights Gram-negative burden and involves in TLR4-NF- κ B signaling, LPS binding to α -syn promotes aggregation and fibrosis. TMAO interferes with diet, liver oxidation, and microbial TMA production from *Anaerococcus*, *Desulfovibrio*, *Clostridium*, and *Providencia*, which crosses the BBB and promotes cognitive impairment. Tryptophan metabolites diagnose toward the kynurenine pathway with increased levels of KYN and 3-hydroxykynurenine and also decreases kynurenine acid, while indole derivatives such as indole-3-propionic acid and indole-3-acetic acid decline and result in weakening of AhR-mediated barrier support. Glial markers such as GFAP and Sox-10 denote enteric gliosis in PD and increasing levels of plasma TNF- α and IFN- γ accompany Verrucomicrobia and Bacteroides



shifts. Specific microbial taxa like *Alistipes*, *Odoribacter*, and Ruminococcaceae subnetworks, correlate with mild cognitive impairment and cooperate to influence approach.

Diet, Microbial Ecology, and Neuroprotection

Diet is the most actionable determinant of microbial composition. High-fiber patterns increase *Prevotella*, Bacteroidetes, and *Lactobacillus*, lower Firmicutes and opportunists such as *Escherichia coli* and *Ruminococcus*, and expand SCFA production. Polyphenols present in large amounts in grapes, berries, cocoa, olives, citrus, apples, almonds, flaxseed, pomegranate, onions, tomatoes, coffee, and tea which inhibits pathogens like *Staphylococcus aureus*, *Salmonella typhimurium*, and *Clostridium* spp while raised levels of *Bifidobacterium* and *Lactobacillus* worsens cognitive decline. Monounsaturated and polyunsaturated fats improve microbial diversity by decreasing the Firmicutes:Bacteroidetes ratio and increases *Bifidobacterium*, Lachnospiraceae, *Roseburia*, and *Akkermansia muciniphila*. Saturated and trans fats helps to promote proinflammatory pathobionts. Fish-oil contains omega-3 PUFAs that elevates beneficial microorganisms and supports synaptic plasticity.

Protein quality improves the tendency of neurochemistry through microbial metabolism. Excess animal protein tend to promotes *Bacteroides*, *Alistipes*, and *Bilophila*. This produce neurotoxic end products. Plant proteins supports in the development of *Bifidobacterium* and *Lactobacillus*, also suppress *Bacteroides fragilis* and *Clostridium perfringens*. Low-protein high-carbohydrate regimens raise aromatic amino acids—tryptophan, tyrosine, phenylalanine—enhancing brain dopamine and serotonin

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synthesis and modulating PD motor control. Dietary fibers serve as microbiota-accessible carbohydrates that are fermented to SCFAs with systemic anti-inflammatory and neuroprotective effects.

Microbial and Hormonal Therapeutics

Probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT) are good strategies to convert dysfunctional flora into health-related configurations. Multi-strain *Lactobacillus* and *Bifidobacterium* formulations improve fecal SCFAs and levels of serum acetate and lactate by improving cognitive test and reduces A β in both clinical and preclinical trials. The prebiotic GV-971 (sodium oligomannate) enhanced cognition in mild-to-moderate AD while correcting dysbiosis and dampening neuroinflammation, demonstrating the therapeutic potential of targeted microbial modulation. TrkB-targeting prebiotics usually inhibits amyloidogenesis and oxidative stress in models.

In Parkinson's disease, microbial enzyme inhibitors and targeted antibiotics that block tyrDC activity leads to increase L-dopa exposure and thus improves motor function and pharmacokinetics. Ghrelin agonists effectively protects dopaminergic neurons and promotes gastric emptying, enhance levodopa absorption by figuring endocrine influence activity within the microbiota-gut-brain axis. Prebiotic fibers, polyphenols, and omega-3 fatty acids further supports barrier integrity and neurotransmitter synthesis. FMT action produces by normalization of microbial composition, improvement in gastrointestinal symptoms, and changes in behavioral deficits in ASD and cognitive decline in AD.

Mechanistic Role of the Microbiota in Causing or Reverting Disease

The microbiota tends to contribute its involvement in both disease propagation and



resilience depending on community structure, host genetics, diet and environmental exposures. SCFA producers belongs to the Lachnospiraceae family or mucin specialists includes, such as *Akkermansia* which modulate ENS function, goblet-cell biology, and vagal signaling, also by supporting gut barrier integrity and neuroimmune homeostasis. Conversely, pathobionts including *Desulfovibrio*, *Bilophila*, and Enterobacteriaceae generate toxic metabolites such as hydrogen sulfide, LPS, and bacterial amyloids that provoke TLR-driven inflammation, oxidative stress, and protein misfolding in the CNS.

Cross-seeding between bacterial amyloids and host proteins integrates microbial ecology with α -synucleinopathy in PD and amyloid pathology in AD. Dysbiosis-induced metabolic dysfunction including altered tryptophan metabolism toward kynurenine, reduced levels of SCFAs, and increased levels of TMAO, develop neuroinflammation, BBB dysfunction, and excitotoxicity. Some of the Therapeutic interventions that restore microbial balance through diet, probiotics, prebiotics, FMT have demonstrated its ability by partially reversing pathological signaling, reducing neuroinflammation, improving neurotransmitter availability, and enhancing behavioral outcomes.

Conclusion

The microbiota–gut–brain axis is a central determinant of neurodevelopmental and neurodegenerative disease. Dysbiosis, barrier dysfunction, and microbial metabolite alterations converge to exacerbate neuroinflammation, proteinopathy, and circuit-level dysfunction in ASD, PD, and AD. Biomarkers such as SCFAs, calprotectin, LPS, TMAO, hydrogen sulfide, sulfite, tryptophan-kynurenine metabolites, glial markers and microbial species profiles con-

tributes for the development and improvement in patient grouping like clinical trials and for understanding pathway mechanisms.

Dietary and microbial interventions tends to offer improvement in clinical associated strategies to restore homeostasis and declines disease progression. Mediterranean, vegetarian, low protein with high carbohydrate and ketogenic diets, in order with probiotics, prebiotics, synbiotics and FMT enrich and improves beneficial microbial taxa, improves barrier integrity, and alters neuroimmune pathways. Future research should focus on longitudinal, strain-level analyses, pathway mechanisms of microbial metabolites, and personalized nutrition-based therapeutics to optimize brain health and resilience.

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