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Bridging the Gap: The Potential Role of the Microbiota-Gut-Brain Axis in Linking Modern Industrial Xenobiotics to Neurological Disorders

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Abstract

The microbiota-gut-brain axis (MGBA) represents a bidirectional neuroendocrine system essential for maintaining metabolic and neurological homeostasis. While dietary macronutrients are known modulators of this axis, the cumulative impact of modern industrial xenobiotics remains insufficiently characterized. This review synthesizes contemporary, multidisciplinary evidence to elucidate how four ubiquitous environmental stressors Particulate Matter (PM2.5), Microplastics (MPs), Inorganic Nanoparticles (NPs), and Non-Nutritive Sweeteners (NNS) synergistically perturb this delicate enteric ecosystem. We integrate independent lines of research to propose a unifying pathological framework: these agents induce profound dysbiosis, significantly depleting beneficial, short chain fatty acid (SCFA) producing taxa (e.g., *Lachnospiraceae*, *Faecalibacterium*) and sharply diminishing the bioavailability of critical neuroactive mediators, including butyrate, GABA, serotonin, and indole derivatives. Concurrently, NNS-driven bacteriostatic shifts, the MP "plastisphere" phenomenon, and NP-induced oxidative mucosal abrasion critically compromise the intestinal barrier. This "leaky gut" facilitates the unrestricted systemic translocation of lipopolysaccharides (LPS) and trimethylamine-N-oxide (TMAO), driving a peripheral Treg/Th17 immune imbalance that propagates via the gut-liver and gut-heart axes directly to the central nervous system (CNS). Crucially, the synthesis of this data points toward a potential "Dual-Hit" mechanism, suggesting that these xenobiotics aggravate neurological pathology through simultaneous mechanisms: acting as direct neurotoxicants via CNS translocation (e.g., NPs crossing the blood-brain barrier to trigger epigenetic reprogramming and amyloid aggregation) while concurrently driving "bottom-up" systemic neuroinflammation. By linking these disruptions to classic neurodegeneration (Alzheimer's, Parkinson's) as well as underexplored pathologies (migraine, epilepsy, restless leg syndrome, and substance use disorders), this review underscores the urgent need for a paradigm shift in environmental neurotoxicology and the development of targeted microbiome-based interventions.

Keywords: microbiota-gut-brain axis; xenobiotics; PM2.5; microplastics; nanoparticles; neurological disorders

1. Introduction

The human gastrointestinal tract harbours a vast and complex community of microorganisms, collectively known as the gut microbiota, which plays a fundamental role in maintaining host physiology. Functioning as a "virtual organ," this ecosystem is integral to nutrient metabolism, immunomodulation, and the maintenance of intestinal barrier integrity. The composition of this microbial community is highly dynamic and susceptible to modulation by a myriad of internal and external factors. Traditionally, host genetics, mode of delivery at birth, antibiotic usage, and most

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significantly, dietary patterns have been identified as the primary determinants of microbial diversity [1] their functional capacity to influence susceptibility to chronic diseases [2].

Crucially, the physiological influence of this microbial community extends far beyond the local enteric environment. Through the circulation of metabolites and immunomodulatory signals, the microbiota engages in intricate crosstalk with distant organs, establishing functional axes such as the gut-liver, gut-lung, and gut-heart axes that are vital for systemic homeostasis. Among these inter-organ networks, the MGBA stands out as a paramount regulator of neurological function. It represents a dynamic, bidirectional communication network linking the enteric ecosystem to the CNS through complex neural, immunological, and endocrine pathways. In a homeostatic state, this axis functions as a critical guardian of neurological health, regulating everything from blood-brain barrier (BBB) integrity to neurogenesis and mood regulation. However, while the impact of established factors like diet is well-documented, the modern industrial era has introduced a novel set of challenges that threaten this delicate equilibrium.

1.1. Physiological Mediators of the Axis: The "Good"

To understand how environmental stressors disrupt neurological function, it is essential to first characterize the mechanisms by which a healthy microbiome supports the brain. The gut microbiota synthesizes a diverse repertoire of metabolites that serve as critical signalling molecules within the MGBA. Among these, bioactive compounds such as SCFAs, aromatic amino acids, and TMAO exert significant regulatory influence over neurological function.

1.1.1. Short-Chain Fatty Acids (SCFAs)

In the large intestine, the primary metabolic output consists of SCFAs (specifically butyrate, propionate, and acetate), derived from the anaerobic fermentation of non-digestible polysaccharides, including resistant starch and dietary fibers. Key taxonomic groups, such as *Lactobacillus*, *Ruminococcus*, *Bifidobacterium*, *Akkermansia*, *Faecalibacterium*, and members of the *Lachnospiraceae* family, are principal drivers of SCFA biosynthesis from complex carbohydrates [3]. Following their biosynthesis, SCFAs undergo transmembrane translocation across the colonic epithelium. This process is primarily facilitated by specialized monocarboxylate transporters (MCTs), including both H+-dependent and sodium-coupled monocarboxylate transporters (SMCTs), which mediate the efficient absorption of these metabolites into the host circulation [4].

SCFAs modulate gastrointestinal mucosal immunity, barrier function, and structural integrity through two primary molecular mechanisms: the activation of G protein-coupled receptors (GPCRs) and the inhibition of histone deacetylases (HDACs). Specifically, SCFAs serve as ligands for free fatty acid receptors (FFAR2 and FFAR3), GPR109a/HCAR2, and GPR164. Upon binding to receptors on enteroendocrine cells, SCFAs stimulate the release of key gut peptides, including peptide YY (PYY) and glucagon-like peptide-1 (GLP-1), alongside neurotransmitters such as gamma-aminobutyric acid (GABA) and serotonin (5-HT). These molecules facilitate neuroendocrine signalling to the central nervous system via both the vagus nerve and systemic circulation [5].

Upon entering the systemic circulation, colon-derived SCFAs exert pleiotropic effects on peripheral tissues. These metabolites augment the thermogenic activity of brown adipose tissue, modulate hepatic mitochondrial biogenesis, and potentiate insulin secretion from pancreatic beta-cells, thereby maintaining global energy homeostasis. Systemically, SCFAs function as potent immunomodulators, regulating the pro-inflammatory cytokine profile by controlling interleukin production and promoting the peripheral differentiation of regulatory T cells (Tregs) [6].

Crucially, SCFAs facilitate neuro-metabolic crosstalk by traversing the blood-brain barrier (BBB) via monocarboxylate transporters expressed in brain endothelial cells. Upon entry, SCFAs bolster BBB structural integrity by upregulating the expression of tight junction proteins, such as occludin and claudin-5. Within the CNS, these metabolites mitigate neuroinflammation by modulating neurotrophic factor expression, fostering neurogenesis, and catalysing serotonin biosynthesis. Furthermore, SCFAs maintain neuronal homeostasis and influence glial cell morphology and

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activation states. Collectively, these multifaceted interactions within the MGBA serve as critical determinants of cognitive function, emotional regulation, and the underlying pathophysiology of neurological disorders [7].

1.1.2. Neurotransmitters and Biogenic Amines

The gut microbiota functions as a significant neuroendocrine organ, synthesizing a wide array of neurotransmitters through both direct and indirect biosynthetic pathways. Several commensal and environmental species most notably *Corynebacterium glutamicum*, *Lactobacillus plantarum*, *Lactococcus lactis*, and *Bacillus subtilis* possess the enzymatic machinery required to catalyse the conversion of L-glutamate into its enantiomer, D-glutamate. This microbial transformation is facilitated by glutamate racemases, representing a critical intersection between bacterial metabolism and host neuro-signalling [8,9]. Subsequently, the biotransformation of D-glutamate into GABA is mediated by glutamate decarboxylase (GAD; EC 4.1.1.15). The metabolic flux of D-amino acids within the central nervous system is significantly modulated by gut-derived microbial activity. Clinically, a notable depletion in plasma D-glutamate concentrations has been identified as a potential biomarker for cognitive decline, particularly in the pathogenesis of Alzheimer's disease [10].

Several studies have highlighted the robust production of GABA by gut microbiota, with notable contributions from *Lactobacillus*, *Bifidobacterium*, and *Bacteroides*, particularly *B. fragilis* [11,12]. Notably, *Escherichia coli K12* demonstrates metabolic versatility by utilizing GABA as a primary substrate for both carbon and nitrogen assimilation. Furthermore, recent taxonomic investigations have identified *Evtepia gabavorous*, a novel species within the *Ruminococcaceae* family characterized by its specialized GABA-consuming phenotype. The identification of such 'GABA-vorous' taxa suggests an intricate competition for neurotransmitter availability within the enteric ecosystem [13]. The metabolic niche of *E. gabavorous* is characterized by an obligate dependency on GABA, with its proliferation strictly contingent upon the presence of GABA-synthesizing commensals such as *Bacteroides fragilis*. While the number of microorganisms capable of interfacing with the GABAergic system remains limited, specific strains exhibit profound neuro-modulatory potential. For instance, *Lactobacillus rhamnosus JB-1* has been shown to modulate the transcriptional expression of GABA receptors (GABARs) within the CNS, an effect correlated with attenuated anxiety and depression-like behaviours [14].

Serotonin, or 5-hydroxytryptamine (5-HT), is a pleiotropic neurotransmitter and hormone that exerts a profound regulatory influence over diverse physiological processes, including gastrointestinal (GI) motility, appetite homeostasis, mood stabilization, and sleep-wake cycles [15]. Notably, the vast majority of systemic 5-HT approximately 90% is biosynthesized within the enteric environment, primarily by specialized enterochromaffin (EC) cells residing in the intestinal mucosa [16]. Specific microbial taxa, including members of the *Enterococcus*, *Streptococcus*, and *Escherichia* genera, synthesize bioactive metabolites that stimulate EC cells to upregulate serotonin biosynthesis [17]. Contemporary research underscores the pivotal role of the gastrointestinal microbiota in 5-HT homeostasis, suggesting that a significant proportion of enteric serotonin is modulated by a diverse consortium of bacteria. This includes *E. coli*, *Hafnia*, *Bacteroides*, *Streptococcus*, *Bifidobacterium*, *Lactococcus*, *Lactobacillus*, *Morganella*, *Klebsiella*, *Propionibacterium*, *Eubacterium*, *Roseburia*, and *Prevotella*, which collectively influence the serotonergic landscape of the host [18].

Dietary tryptophan, an essential amino acid, serves as the primary substrate for the biosynthesis of 5-HT, a process facilitated by the enzymatic activity of specific microbial taxa, most notably *Candida* and *Escherichia* species [19]. The delicate balance of this axis is critical; perturbations are closely implicated in the pathogenesis of IBD. Histopathological analyses of tissues from patients with Crohn's disease and ulcerative colitis reveal a marked proliferation of serotonin-secreting cells, and this elevation in serotonin-immunoreactivity underscores the potential for neuro-endocrine dysregulation to drive chronic intestinal inflammation [20]. Conversely, in healthy individuals, *Clostridium perfringens* optimally modulates serotonin synthesis through its interaction with host-derived tryptophan hydroxylase (TPH), the rate-limiting enzyme in the 5-HT biosynthetic pathway

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[21]. Beyond its canonical gastrointestinal functions, serotonin serves as a potent immunomodulator and a regulator of glial cell dynamics within both the enteric and central nervous systems.

Furthermore, the gut microbiota catabolizes tryptophan into bioactive indole derivatives via enzymatic routes involving tryptophan monooxygenase and indole-3-acetamide hydrolase. Notably, indole-3-aldehyde, synthesized by *Lactobacillus* species, functions as a ligand for aryl hydrocarbon receptors (AhR) on mucosal and immune cells. This activation precipitates the secretion of interleukin-22 (IL-22) and the subsequent release of antimicrobial peptides, thereby fortifying intestinal barrier integrity [22]. Specific commensal species, including *Lactobacillus reuteri*, *Lactobacillus johnsonii*, and *Lactobacillus murinus*, facilitate the catabolism of tryptophan into indole derivatives. These metabolites serve as critical signalling cues for the lineage commitment and differentiation of T cell subsets [23].

In parallel, the biogenic amine histamine exerts a multifaceted regulatory influence over host homeostasis, most notably in the promotion of wakefulness and the modulation of appetitive and motivational behaviours. The biosynthesis of histamine within the enteric environment is attributed to a phylogenetically diverse consortium of bacteria, comprising *Lactobacillus* spp., *Lactococcus lactis*, *Oenococcus oeni*, *Pediococcus parvulus*, *Streptococcus thermophilus*, *Enterobacter* spp., *Citrobacter freundii*, and *Hafnia alvei*, alongside opportunistic pathogens such as *Morganella morganii* and *Klebsiella pneumoniae* [12]. A comprehensive summary of these key gut microbiota-derived metabolites, their primary biosynthetic taxa, and their specific neuroprotective roles within the MGBA is detailed in **Table 1**.

Table 1. Key Gut Microbiota-Derived Metabolites and Their Neuroprotective Functions within the MGBA.

Metabolite	Primary Biosynthetic Taxa	Neuroprotective & Homeostatic Functions	References
Butyrate	*Faecalibacterium prausnitzii*, *Roseburia* spp., *Eubacterium rectale*, *Clostridium butyricum*, *Coprococcus*, *Butyricicoccus pullicaecorum*	Attenuates ASD-like endophenotypes; enhances memory in advanced Alzheimer's disease stages; promotes neuroprotection, learning, and preserves cognitive function.	[24–26]
Propionate	*Bacteroides fragilis*, *B. vulgatus*, *B. thetaiotaomicron*, *Prevotella copri*, *Veillonella parvula*, *V. alcalescens*, *Akkermansia muciniphila*	Ameliorates motor and non-motor abnormalities in Parkinson's disease models.	[27]
γ-Aminobutyric Acid (GABA)	*Lactobacillus brevis*, *L. plantarum*, *L. buchneri*, *L. paracasei*, *Bifidobacterium adolescentis*, *B. dentium*, *B. infantis*	Prevents neurodegeneration; mitigates oxidative stress and mitochondrial dysfunction (deficits are linked to PD neuropathology); attenuates ASD severity.	[28–30]
Serotonin (5-HT)	*Ligilactobacillus ruminis*, *Limosilactobacillus mucosae*, *Escherichia* spp., *Enterococcus* spp., *Klebsiella pneumoniae*, *Streptococcus* spp.	Regulates sleep-wake cycles, mood stabilization, and cognitive processes.	[31]
Kynurenine	*Actinobacteria*, *Bacteroides*, *Firmicutes*, *Fusobacteria*, *Proteobacteria*	Functions as an NMDA receptor antagonist, conferring neuroprotection by blocking	[32]

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		excessive glutamate excitotoxicity.	
Indole Propionic Acid (IPA)	*Escherichia coli*, *Clostridium sporogenes*, *Bacteroides ovatus*, *B. thetaiotaomicron*	Exerts potent antioxidant effects; scavenges reactive oxygen species (ROS) to protect neuronal integrity and attenuates central neuroinflammation.	[33,34]
Indole Acetic Acid (IAA)	*Intestinibacter bartlettii*, *Blautia hydrogenotrophica*, *Lactobacillus reuteri*, *L. acidophilus*, *Bifidobacterium* spp., *Faecalibacterium*	Attenuates neuroinflammatory responses in microglia and suppresses macrophage production of pro-inflammatory cytokines.	[35,36]

1.2. The Modern Industrial Shift: The "Bad"

While the MGBA evolved to process natural dietary components, the modern industrial environment has introduced a novel class of persistent stressors that challenge this delicate equilibrium. Specifically, the pervasive infiltration of microplastics (MPs), the ubiquity of inorganic nanoparticles (NPs) (both food-grade and environmental), the massive consumption of artificial sweeteners, and the rising burden of air pollution (PM2.5**)** represent a "tetrad" of modern disruptors.

1.2.1. The Xenobiotic Paradigm

This review classifies these agents as **xenobiotics**: foreign compounds that the human gut has not evolved to process. Despite their differing origins whether inhaled as particulate matter or ingested as a food additive these stressors converge on a common pathological pathway: the disruption of mucosal homeostasis. This leads to a state of chronic dysbiosis and barrier dysfunction, facilitating the systemic translocation of inflammatory mediators.

1.2.2. Scope and Synthesis

To provide a more comprehensive overview, this synthesis extension beyond classical neurodegenerative diseases (Alzheimer's, Parkinson's) to include epilepsy, migraine, restless leg syndrome, and substance use disorders conditions where the intersection of environmental toxicology and the gut-brain axis is significantly less explored. It is important to note that while substantial evidence exists for xenobiotic impact on the gut, and separate evidence links gut dysbiosis to these neurological disorders, research findings that directly establish the role of these specific stressors (MPs, PM2.5, NPs, NNSs) in causing neurological diseases *by* altering gut microbiome homeostasis are lacking. Therefore, this review synthesizes the role of modern industrial byproducts in developing and aggravating neurological disorders by bridging these published independent studies to propose a cohesive mechanistic pathway.

2. Effect of Modern Food Additives: Non-Nutritive Sweeteners

The modern diet is characterized by the excessive consumption of industrial sweeteners, particularly non-nutritive sweeteners (NNS). NNS offer a distinct metabolic advantage over conventional caloric sweeteners due to their negligible caloric density and lack of a direct glycaemic response. However, given their ubiquity as modern food additives, substantial research has emerged investigating the capacity of these compounds to act as potent modulators of the composition and function of the gut microbiota [37,38].

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2.1. Saccharin and Metabolic Dysregulation

Synthetic NNS, such as saccharin, have been shown to directly modulate the composition and metabolic function of the gut microbiota. This induction of gut dysbiosis appears to drive the downstream glucose intolerance phenotype observed in mammalian hosts. Clinically, NNS consumption exhibits a significant positive correlation with several biomarkers of metabolic syndrome, including markers of obesity (increased weight and waist-to-hip ratio) and impaired glycaemic control (elevated fasting blood glucose, glycosylated haemoglobin (HbA1c), and diminished glucose tolerance test (GTT) performance. Furthermore, elevated serum alanine aminotransferase (ALT) levels suggest secondary hepatic involvement, potentially linked to non-alcoholic fatty liver disease (NAFLD) a condition intricately tied to systemic inflammation and gut barrier permeability.

In a controlled intervention, participants consuming the FDA's maximal acceptable daily intake (ADI) of commercial saccharin (5 mg/kg body weight) for just seven days exhibited profound microbial shifts. These changes were characterized by a 20-fold relative increase in *Bacteroides fragilis* (order *Bacteroidales*) and *Weissella cibaria* (order *Lactobacillales*), contrasted by an approximately tenfold reduction in *Candidatus arthromitus* (order *Clostridiales*) [39].

2.2. Comparative Impacts of Modern Sweeteners

Recent comparative studies highlight the divergent effects of various sweeteners on the enteric landscape. Alex et al. (2025) utilized mini-bioreactor arrays to evaluate the differential impacts of five prevalent non-nutritive sweeteners including Acesulfame K, Rebaudioside A, Saccharin, Sucralose, and Xylitol on gut microbial diversity. Family-level taxonomic analysis revealed that while all compounds perturbed the microbial equilibrium, the synthetic sweetener sucralose induced the most profound dysbiosis. Specifically, sucralose fostered the enrichment of the *Enterobacteriaceae* family, including pathogenic genera such as *Escherichia* and *Citrobacter*, which are frequently implicated in driving intestinal inflammation.

Conversely, the naturally derived sweeteners Rebaudioside A (found in the Stevia plant) and Xylitol promoted the proliferation of *Lachnospiraceae* and *Ruminococcaceae*. These taxa are critical for the biosynthesis of SCFAs, such as butyrate, which are essential for maintaining gut barrier integrity, modulating systemic inflammation, and preserving metabolic homeostasis along the gut-brain axis [40]. To provide a comprehensive overview of these dietary impacts, Table 2 summarizes recent experimental and clinical findings detailing the specific taxonomic perturbations induced by various non-nutritive sweeteners and food additives.

Note on Processed Caloric Sweeteners It is worth noting that metabolic disruption is not exclusive to synthetic xenobiotics. High Fructose Corn Syrup (HFCS), while derived from natural sources, represents a highly processed industrial additive that similarly disrupts gut homeostasis [41]. Excessive intake of free fructose monomers found in HFCS has been shown to overwhelm intestinal transporters, reaching the colon to degrade the mucus layer and increase intestinal permeability, mirroring the endotoxemia observed with synthetic stressors [42,43].

Table 2. Impact of Non-Nutritive Sweeteners (NNS) and Dietary Additives on Gut Microbial Architecture Across Human and Murine Models.

Study Model & Exposure Paradigm	Taxonomic Perturbations & Dysbiosis Profile	References
Female SD rats (8 weeks old, n=150); exposed to high-fat diet + aspartame (5-7 mg/kg)	↓ *Enterococcaceae*, *Enterococcus*, *Parasutterella*; ↑ *Clostridium cluster IV*	[44]
Human cohort (n=120, divided into 4 groups); aspartame, saccharin, sucralose, or stevia	↓ Abundance of *Porphyromonas*, *Prevotella nanceiensis*	[45]

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Pregnant C57BL/6 mice (8 weeks old); fed sucralose (0.1 mg) + acesulfame-K (0.25 mg)	In offspring microbiome: ↑ *Firmicutes*; ↓ *Akkermansia muciniphila*	[46]
Male C57BL/6J mice (8 weeks old); acesulfame-K (150 mg/kg body weight/day for 8 weeks)	↓ *Clostridiaceae*, *Lachnospiraceae*, *Ruminococcaceae*	[47]
Human volunteers (n=47, ages 18-35); administered sucralose (48 mg/day for 10 weeks)	↑ Abundance of *Blautia coccoides*	[48]
Male C57BL/6J mice (SPF, age 28 days); sucralose (0.0003-0.3 mg/mL for 16 weeks)	Jejunum/Ileum/Colon: ↑ *Tenacibaculum*, *Ruegeria*, *Staphylococcus*, *Allobaculum* Cecum: ↓ *Lachnoclostridium*, *Lachnospiraceae* (in high dose group)	[49]
Pregnant C57BL/6 mice; high-fat diet (4 weeks) then sucralose (0.1 mg/mL for 6 weeks)	Maternal: ↑ *Firmicutes*, *Proteobacteria*; ↓ *Bacteroidetes* Post-HFD: enhanced reduction in *Proteobacteria* compared to control	[50]
Mice (5 weeks old); standard diet + sucralose vs. high-fat diet (HFD) + sucralose	↑ *Firmicutes*; ↓ *Bacteroidetes* (Note: *Firmicutes* also increased in the standard HFD group)	[51]
Male C57BL/6J mice (8 weeks old); sucralose (15 mg/kg body weight/day for 8 weeks)	Faecal microbiota: ↓ *Clostridium cluster XIVa*	[52]
Male C57BL/6 mice; sucralose in drinking water (5 mg/kg body weight/day)	3 months: ↑ *Ruminococcus*; ↓ *Lachnospiraceae*, *Staphylococcus*, *Bacillus* 6 months: ↑ *Akkermansia*, *Roseburia*; ↓ *Streptococcus*, *Lachnospiraceae*	[53]
Male C57BL/6J mice (8 weeks old); saccharin in drinking water (0.3 mg/mL)	3 months: ↑ *Akkermansia*, *Oscillospira*, *Corynebacterium*; ↓ *Anaerostipes*, *Ruminococcus* 6 months: ↑ *Corynebacterium*, *Roseburia*, *Turicibacter*; ↓ *Ruminococcus*, *Dorea*	[54]

3. Effect of Microplastics

The gut microbiota, a central regulator of metabolic homeostasis, nutrient assimilation, and systemic immune modulation, is increasingly recognized as a primary target for microplastic (MP) toxicity. Growing evidence suggests that MP exposure precipitates intestinal dysbiosis, characterized by a deleterious shift in the ratio of commensal to pathogenic taxa. Such microbial perturbations can compromise intestinal barrier integrity, attenuate immune responsiveness, and heighten susceptibility to diverse gastrointestinal and systemic disorders [55–57].

3.1. Exposure Pathways and Dysbiosis

Dietary ingestion via seafood, salt, and water represents a primary exposure pathway. Experimental evidence suggests that polyethylene ingestion increases the relative abundance of *Firmicutes* and *Bacteroidetes* [58,59]. In Indonesian coastal and highland populations, MP contamination correlated with the prevalence of *Roseburia*, *Clostridium*, and *Prevotella*, alongside an enrichment of genes encoding plastic-degrading enzymes within the gut metagenome [60].

Recent investigations into chronic polyethylene (PE) microplastic exposure have revealed significant disruptions to infant gut microbiota and intestinal barrier function. Prolonged PE ingestion facilitates the proliferation of opportunistic pathobionts, most notably members of the *Dethiosulfovibrionaceae* and *Enterobacteriaceae* families, concurrently resulting in a marked reduction in enteric butyrate concentrations [61]. Furthermore, the biotransformation of microplastics, specifically

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polyethylene terephthalate (PET), evaluated using dynamic gastrointestinal simulators, demonstrated significant modulation of the human colonic microbiota and evidence of microbial colonization on plastic surfaces, suggesting potent biofilm formation (the "plastisphere") within the enteric environment [62]. The dual physical and microbiological threat posed by MPs at the intestinal mucosal interface is comprehensively illustrated in **Figure 1.**

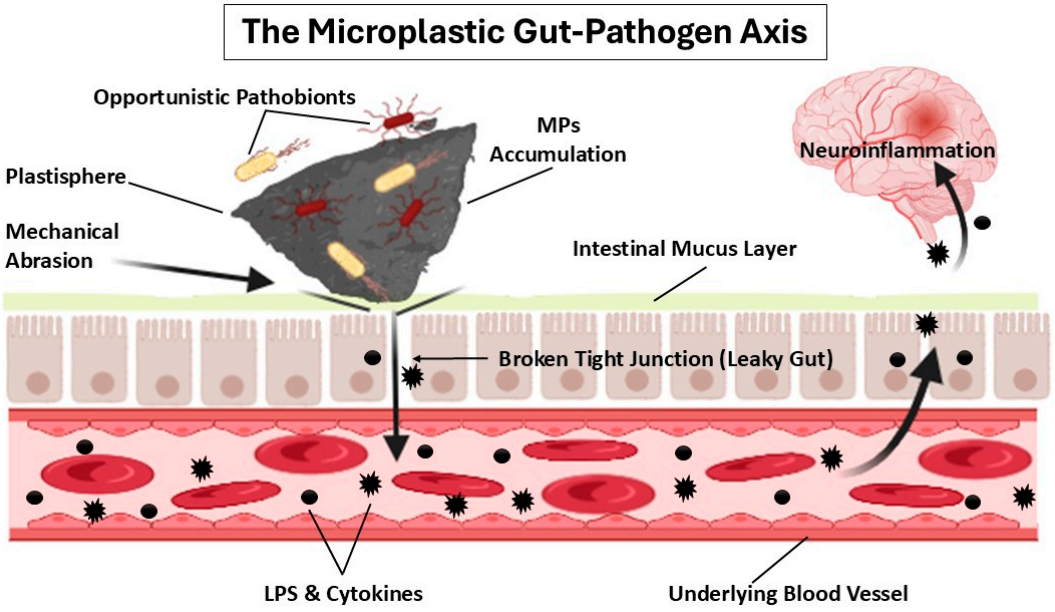

Figure 1. The Microplastic-Gut-Pathogen Axis. Ingested microplastics act as physical vectors (the "plastisphere") for opportunistic pathobionts, facilitating their colonization in the enteric ecosystem. The jagged plastic fragments mechanically abrade the protective intestinal mucus layer and disrupt epithelial tight junctions, creating a "leaky gut." This structural compromise allows pathogen-derived lipopolysaccharides (LPS) and pro-inflammatory cytokines to translocate into the systemic circulation, ultimately breaching the blood-brain barrier and triggering profound neuroinflammation.

3.2. Systemic Inflammation and Immune Dysregulation

The translocation of microbial-derived products, such as lipopolysaccharides (LPS), into the systemic circulation secondary to MP-induced mucosal damage triggers a robust pro-inflammatory cascade. This chronic systemic inflammation serves as a primary driver of immune dysregulation, significantly elevating the risk for autoimmune pathologies, including rheumatoid arthritis, systemic lupus erythematosus (SLE), and inflammatory bowel disease (IBD) [63]. Intestinal dysbiosis compromises the induction and differentiation of regulatory T cells (Tregs), which are indispensable for maintaining peripheral immune tolerance. A disruption in the homeostatic equilibrium between immunosuppressive Tregs and pro-inflammatory Th17 cells often termed the Treg/Th17 balance is a critical factor in the exacerbation of neuroinflammatory conditions such as multiple sclerosis (MS) [64]. Furthermore, the clinical progression of these conditions is often exacerbated by deleterious mutations in *FOXP3* the master transcription factor governing Treg lineage commitment precipitating a profound loss of immunological self-tolerance [65].

3.3. The Gut-Liver and Gut-Heart Axes: Systemic Conduits to Neuroinflammation

The 'gut-liver axis' provides a critical framework for evaluating the systemic toxicity of MPs. As the primary site for the metabolism of xenobiotics, the liver is uniquely susceptible to MP-induced injury. In vitro studies utilizing human liver organoids demonstrate that exposure to polystyrene MPs precipitates significant hepatotoxicity, characterized by lipo-toxicity, oxidative stress, and a robust inflammatory response [66]. Crucially, this hepatic impairment diminishes the liver's capacity

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to detoxify circulating neurotoxins (e.g., ammonia) and amplifies the systemic release of pro-inflammatory cytokines. These peripheral inflammatory signals subsequently compromise the integrity of the BBB, initiating neuro-inflammatory cascades within the CNS.

Similarly, the 'gut-heart axis' is compromised by MP-induced endotoxemia. Increased intestinal permeability facilitates the systemic translocation of deleterious metabolites, such as TMAO, into the portal circulation. Upon reaching the liver, these compounds exacerbate chronic systemic inflammation, subsequently compromising cardiovascular integrity [67,68]. Critically, recent clinical observations reveal that MP accumulation in carotid artery plaques is associated with a significantly elevated risk of major adverse cardiovascular events (MACE), demonstrating a hazard ratio of 4.53 [69]. This cardiovascular deterioration is inextricably linked to neurological decline; endothelial dysfunction and compromised vascular health inevitably extend to the cerebral microvasculature. Furthermore, microbiota-derived metabolites like TMAO not only drive atherosclerosis but are also emerging as potent promoters of brain aging and neuroinflammation, actively disrupting BBB tight junctions and paving the way for neurological disorders.

3.4. The Gut-Brain Axis and Neurotoxicity

Beyond indirect systemic inflammation, emerging evidence suggests that MPs may also infiltrate the CNS directly via the olfactory pathway. A post-mortem analysis in Brazil identified synthetic polymers in the olfactory bulb tissues of 53% of the cohort, providing a plausible mechanism for MP translocation to the brain, bypassing the BBB and raising critical concerns regarding localized neurotoxicity [70]. To illustrate the breadth of these xenobiotic impacts, **Table 3** summarizes recent human cohorts and murine models demonstrating the profound gut microbial architectural shifts induced by varying forms of microplastic exposure.

Table 3. Impact of Microplastic (MP) Exposure on Gut Microbial Architecture in Human Cohorts and Murine Models.

Study Model & Exposure Paradigm	Taxonomic Perturbations & Dysbiosis Profile	References
In vitro human GI digestion (n=6 volunteers, ages 20-27); PCL (150 nm) & PLA (75 nm) MPs	↓ Richness and α-diversity; ↓ *Bifidobacterium*, *Faecalibacterium*; ↑ Pathogenic taxa (e.g., *Prevotella*)	[71]
Student cohort (n=60); exposed via disposable plastic tableware (3 hot meals/day)	↓ *Bacteroidota*, ↑ *Actinobacteriota*; ↓ *Faecalibacterium*, ↑ *Blautia*	[72]
Occupational cohort (n=40; plastic factory workers vs. low exposure); Polyurethane predominantly detected	↑ *Bifidobacterium*, *Streptococcus*, *Sphingomonas*; ↓ *Ruminococcus*, *Dorea*, *Fusobacterium*, *Coprococcus*	[73]
Preschool children cohort (n=69); Stool MPs (PVC, PET, PE, PA6) at 425.0 μg/kg/day	↓ α-diversity; Altered probiotic taxa including ↓ *Parabacteroides*, *Alistipes*	[74]
Adult cohort (n=39, ages 25-69); Stool MPs (PE, PVC, PS, PP, PA6)	↑ *Enterobacteriaceae*, *Escherichia coli*; ↓ *Faecalibacterium prausnitzii*	[75]
Male C57BL/6 mice; Polystyrene (PS) MPs (0.05–0.1 μm, 9–10 μm, or mixture at 100 ppb)	Mixed PS: ↑ *Campylobacterota*; Individual PS: ↓ *Proteobacteria*, *Cyanobacteria*; Small PS (0.1 μm): ↑ *Actinobacteria*	[76]
College student cohort (n=125, ages 18-30); Take-out food	Dose-dependent altered abundances of *Firmicutes*, *Bacteroidota*, *Blautia*,	[77]

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consumers (9 MP types detected)	*Lachnospiraceae*, *Faecalibacterium*, *Bacteroides*, and *Bifidobacterium*

4. Effect of Nanoparticles

The rapid expansion of nanotechnology has introduced a paradigm shift in active and intelligent food packaging through enhanced barrier functions and antimicrobial surface modifications. However, the propensity for nanomaterials (NMs) to migrate from polymeric matrices into food simulants is well-documented, facilitating a direct pathway for human internal exposure [78]. Consequently, the gastrointestinal tract is increasingly exposed to both intentional food-grade additives and unintentional anthropogenic nanoparticles. These particles possess unique physicochemical properties—specifically their high surface-area-to-volume ratio—that allow them to interact directly with the enteric microbiota and bypass physiological barriers [79].

4.1. Food-Grade Nanoparticles and Packaging Migrants

Food-grade nanomaterials and packaging migrants -such as Titanium Dioxide (TiO2/E171), Silver Nanoparticles (AgNPs), and Zinc Oxide (ZnO) exert a profound influence on the intestinal microbial landscape. Zinc oxide nanoparticles, frequently utilized for their potent antimicrobial efficacy within food packaging systems, induce significant taxonomic perturbations [80]. Following a 28-day administration of ZnO NPs (1000 mg/kg) in murine models, responses exhibited clear sexual dimorphism: male rats displayed an expansion of the *Firmicutes* phylum and contraction of *Bacteroidetes*, whereas female rats displayed a contraction in *Firmicutes* alongside a significant proliferation of *Verrucomicrobiota* and *Lactobacillus* probiotics [81].

Similarly, silver nanoparticles (AgNPs) extensively utilized against multi-drug-resistant pathogens demonstrate persistent modulatory effects. Chronic, escalating exposure (0.1, 2, 40 μg) induces a characteristic shift in the *Firmicutes*-to-*Bacteroidetes* (F/B) ratio, driven primarily by an enrichment of *Firmicutes* [82]. Shorter-term interventions (0.5–2.5 mg/kg) corroborate this trend, precipitating a notable expansion of the *Lachnospiraceae* family alongside a depletion of *Bacteroidetes* [83]. Finally, TiO2 NPs significantly reshape the enteric environment; experimental exposures (2, 10, 50 mg/kg) resulted in the selective enrichment of *Levilactobacillus* and *Allobaculum*, contrasted by a marked reduction in the *Clostridiaceae* family [84].

Beyond the gut level, systemic bioaccumulation drives further pathology. For example, longitudinal assessments of silver nanoparticles (AgNPs) indicate that chronic systemic exposure facilitates significant bioaccumulation within the hepatic and splenic parenchyma, precipitating marked inflammation and deleterious histopathological alterations that compound the body's overall systemic inflammatory burden [85].

4.2. Unintentional Anthropogenic Nanoparticles

Beyond intentional additives, the gut is increasingly exposed to unintentional nanoparticles derived from environmental pollution and industrial processes. Investigations in zebrafish models reveal that exposure to Carbon Black nanoparticles (CBNPs) precipitates a marked reduction in intestinal flora diversity and profoundly alters core microbial populations. This dysbiosis is coupled with increased permeability of the intestinal mucosal barrier—driven by the dysregulation of tight junction-related genes and concurrent hepatic insult, characterized by vascular degeneration and lipid accumulation [86] Similarly, ingested silica nanoparticles have been observed to potentiate intestinal inflammation [87] by activating the NLRP3 inflammasome, and exacerbate secondary white matter injury by disrupting the blood–brain barrier, inducing neuroinflammation, and interfering with nerve regeneration [88].

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4.3. Mechanisms of Nanoparticle-Induced MGBA Disruption

Metallic and metal-oxide nanoparticles act as primary drivers of cellular homeostatic disruption. Locally within the gastrointestinal tract, NPs (particularly ZnO NPs) catalyze the overproduction of reactive oxygen species (ROS) across diverse cellular lineages. This oxidative surge, coupled with subsequent DNA fragmentation, presents a genotoxic and pro-inflammatory profile that damages the structural and functional integrity of the intestinal epithelial barrier [89]. Furthermore, contemporary research demonstrates that titanium dioxide nanoparticles exhibit the capacity for transepithelial translocation from the gastrointestinal lumen to distal organs, including the liver, kidneys, and CNS, following oral ingestion [90].

Once inside the central nervous system, these translocated nanoparticles (including titanium dioxide, nanosilica, and nanosilver) function as potent catalysts for neurodegenerative pathologies. Contemporary research reveals a convergent mechanism of neurotoxicity driven by epigenetic reprogramming. Specifically, NP exposure precipitates aberrant DNA methylation and dysregulates ryanodine receptor-Ca2+ signalling within the murine brain. These molecular shifts culminate in lysosomal dysfunction and the subsequent attenuation of autophagic flux in neurons. Critically, this proteostatic failure compromises the clearance of neurotoxic aggregates, specifically β-amyloid and hyperphosphorylated tau (p-Tau). The resultant accumulation of these aggregates ultimately drives the clinical manifestation of spatial cognition and memory deficits [91]. The complex sequence of events, from initial enteric translocation to subsequent neuronal epigenetic and proteostatic failure, is visually summarized in **Figure 2**. The diverse taxonomic perturbations induced by various food-grade and environmental nanoparticles across different in vivo models are systematically summarized in **Table 4**.

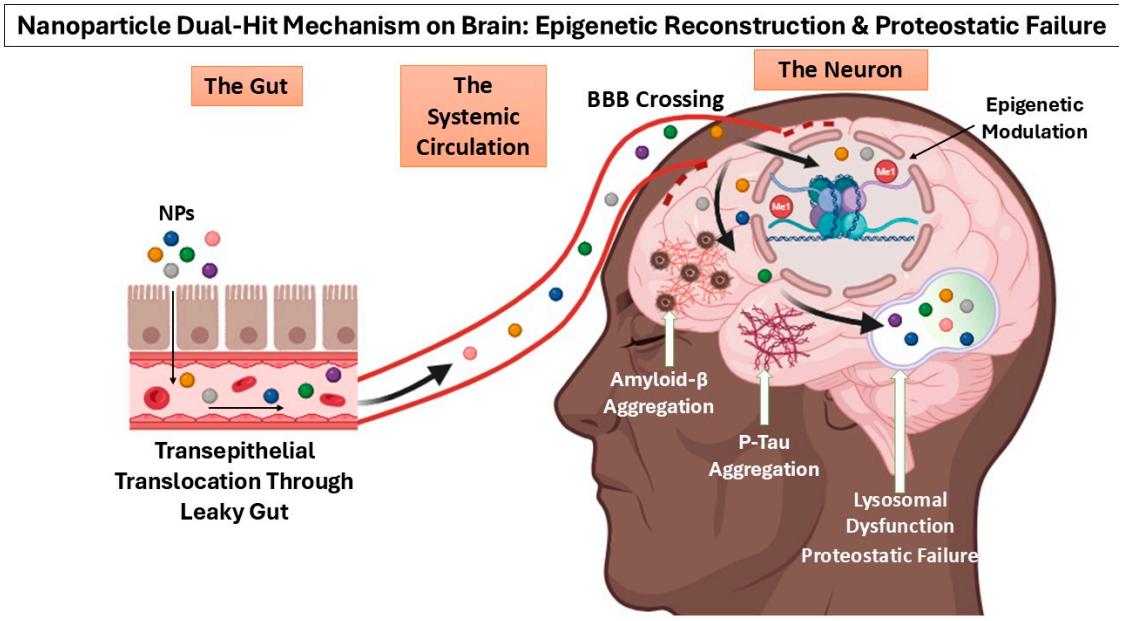

Figure 2. The Nanoparticle Dual-Hit Hypothesis. This diagram illustrates the two-pronged mechanism by which inorganic nanoparticles (NPs) drive neurodegeneration. The first "hit" (Hit-1) is direct: NPs physically translocate into the central nervous system through systemic circulation (breaching the blood-brain barrier) or olfactory pathways, acting as immediate neurotoxicants that induce epigenetic reprogramming and proteostatic failure. The second "hit" (Hit-2) is indirect: NPs profoundly alter the gut microbiome and enteric nervous system, compromising the mucosal barrier to unleash a systemic wave of inflammatory mediators. This gut-derived neuroinflammatory storm traverses the gut-brain axis, severely exacerbating the direct toxic effects of the accumulated particles in the brain.

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Table 4. Impact of Inorganic Nanoparticle (NP) Exposure on Gut Microbial Architecture Across In Vivo Models.

Study Model & Exposure Paradigm	Taxonomic Perturbations & Dysbiosis Profile	References
Female rats (prenatal exposure); TiO2 NPs (5 mg/kg, GD 5-18)	↑ *Clostridiales* (GD 10); ↓ *Dehalobacteriaceae* (GD 17)	[92]
Rats; oral TiO2 NPs (29nm, 0-50 mg/kg/day for 90 days)	↑ *Lactobacillus reuteri*; ↓ *Romboutsia*	[93]
Mice; oral TiO2 NPs (100 mg/kg/day for 28 days)	↑ *Actinobacteria, Proteobacteria*; ↓ *Firmicutes, Bacteroidetes*	[94]
Rats and Mice; oral AgNPs (2.5 or 3.6 mg/kg for 7-14 days)	Shifted *Firmicutes/Bacteroidetes* (F/B) ratio	[95,96]
Piglets; oral ZnO NPs (600 mg/kg for 14 days)	Ileum: ↑ *Streptococcus*, ↓ *Lactobacillus*; Colon: ↑ *Lactobacillus*, ↓ *Oscillospira, Prevotella*	[97]
Broiler chickens; oral ZnO NPs (5 mg/kg for 42 days)	↑ *Ruminococcaceae, Bacteroidaceae*; ↓ *Lachnospiraceae, Lactobacillaceae, Rikenellaceae*	[98]
Rats; oral TiO2 NPs (2-50 mg/kg/day for 30 days)	↑ *Lactobacillus gasseri, Turicibacter*; ↓ *Veillonella*	[99]
Male C57BL/6JAusb mice (5-6 weeks old); oral TiO2 NPs (drinking water, 0-50 mg/kg for 3 weeks)	↑ *Lactobacillus, Allobaculum*; ↓ *Adlercreutzia*, unclassified *Clostridiaceae*	[84]
C57BL/6 mice; oral AgNPs (0.1, 2, 40 μg for 120 days)	↑ *Firmicutes*; ↓ *Bacteroidetes*	[82]
Wistar rats; oral AgNPs (7nm, 100 mg/kg for 28 days)	↑ *Bacteroidota*; ↓ *Verrucomicrobia, Proteobacteria, Lactobacillaceae*	[100]
Wistar albino rats; oral ZnO NPs (1000 mg/kg for 28 days)	Males: ↑ *Firmicutes*, ↓ *Bacteroidetes*; Females: ↓ *Firmicutes*, ↑ *Verrucomicrobia*	[81]

5. Effect of Air Pollution: Particulate Matter (PM2.5)

Fine particulate matter (PM2.5) atmospheric particulates with a diameter of 2.5 μm or less derived primarily from combustion activities, industrial processes, and natural sources like wildfires has emerged as a significant contributor to global health risks [101]. The infiltration of these particulates across the pulmonary-capillary barrier into the systemic circulation is a well-established driver of obstructive respiratory illnesses [102,103], cardiovascular dysfunction [104], and oncogenic transformations [105]. This episodic and chronic exposure is particularly devastating at the extremes of the age spectrum, affecting the immature respiratory systems of children and the diminished compensatory mechanisms of the elderly [106]. However, its specific capacity to perturb the gastrointestinal tract and the gut-brain axis represents a newly recognized dimension of its systemic toxicity.

5.1. The Lung-Gut Exposure Route and Barrier Dysfunction

Inhaled PM2.5 undergoes gastrointestinal translocation primarily via the mucociliary escalator; particulates trapped within the tracheobronchial mucosa are cephalad-propelled to the oropharynx and subsequently ingested. Compelling experimental and epidemiological evidence indicates that this direct enteric exposure severely compromises intestinal barrier integrity [107].

Xie et al. demonstrated that chronic exposure to elevated PM2.5 concentrations in murine models induces a dose- and duration-dependent upregulation of pro-inflammatory cytokines (IL-6, IL-10, IL-1β, and TNF-α). This inflammatory surge was associated with significant structural insult

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to the colonic mucosa. Mechanistically, this pathogenesis is driven by a linear, dose-dependent downregulation in the expression of critical transmembrane tight junction proteins, specifically Occludin and Zonula Occludens-1 (ZO-1), underscoring a systematic compromise of the intestinal epithelial barrier [108].

5.2. Profound Dysbiosis and Metabolic Perturbation

In vivo investigations utilizing various murine models indicate that PM2.5 exposure induces significant perturbations in the intestinal microbiota and its associated metabolome. In longitudinal studies, male C57BL/6 and BALB/c models subjected to atmospheric PM2.5 inhalation trigger a systemic restructuring of the microbial architecture. At the phylum level, this is characterized by a significant contraction in the relative abundance of *Bacteroidetes*, contrasted by a marked compensatory expansion of the *Firmicutes* and *Cyanobacteria* phyla [109].

At the genus level, particulate insult precipitates a marked depletion of commensal SCFA producers, most notably *Prevotella*, *Bacteroides*, and *Tremihum*, alongside the enrichment of opportunistic genera such as *Lactobacillus*, *Parabacteroides*, *Oscillospira*, *Coprococcus*, and *Desulfovibrio* [110]. Furthermore, PM2.5 exposure significantly reduces vitamin B12-associated genera, including *Faecalibacterium*, *Citrobacter*, and *Collinsella*. The suppression of these specific taxa disrupts the vitamin B12 biosynthetic pathway, potentially driving the aberrant secretion of neurotransmitters and contributing directly to neuro-metabolic dysfunction [111].

5.3. Neuroinflammatory and Neurodegenerative Consequences

Sustained pro-inflammatory signalling, driven by the vascular translocation of fine particulates and gut-derived endotoxins, serves as a catalyst for systemic homeostatic disruption that ultimately reaches the CNS. Substantial evidence identifies PM2.5 as a critical environmental determinant in the aetiology of neurodegenerative pathologies.

Notably, cognitive impairment a primary prodromal manifestation of Alzheimer's disease (AD) is strongly associated with chronic PM2.5 exposure, with geriatric populations in high-pollution locales exhibiting accelerated cognitive decline [112]. These clinical observations are corroborated by a landmark cohort study of 602 autopsy-confirmed cases, which demonstrated that elevated PM2.5 exposure significantly correlates with increased severity of Alzheimer's Disease Neuropathologic Change (ADNC) and progressed clinical markers of dementia [113].

Similarly, a longitudinal cohort study in Ontario demonstrated that even low-level PM2.5 exposure (3.8 μg/m3) significantly correlates with an elevated risk of Parkinson's disease (PD) and increased PD-related hospitalization rates [114]. Furthermore, research in New York indicates that chronic PM2.5 exposure precipitates clinical deterioration in existing PD patients. Emerging data suggest that these deleterious neurodegenerative effects are intrinsically linked to the dysbiosis-induced breakdown of the gut-brain axis and modulated by the specific physicochemical composition of the translocated particulates [115]. A synthesis of recent epidemiological and experimental studies detailing the specific dysbiotic profiles and taxonomic shifts induced by PM2.5 exposure is provided in **Table 5**.

Table 5. Impact of Particulate Matter (PM2.5) Exposure on Gut Microbial Architecture in Human Cohorts and Murine Models.

Study Model & Exposure Paradigm	Taxonomic Perturbations & Dysbiosis Profile	References
Southwest China cohort (n=1583); long-term exposure to PM2.5	↓ α-diversity; ↓ *Bacteroidetes*, ↑ *Proteobacteria*	[116]
Guangdong Province cohort (n=3267, ages 40–75); exposure to PM2.5	↓ *Bacteroidetes*; ↑ *Actinobacteria*, *Firmicutes*, *Ruminococcus*	[117]

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Shanghai maternal–child pairs (n=361); prenatal PM2.5 exposure	Validation of seven PM2.5-correlated genera: *Ruminococcus gnavus* group, *Romboutsia*, *Burkholderiaceae*, *Blautia*, *Alistipes*, *Parabacteroides*, and *Bacteroides*	[118]
Healthy seniors (n=76, ages 60–69); exposure to PM2.5	↓ α-diversity; ↑ *Lachnoclostridium*, *Streptococcus*, *Veillonella*; ↓ *Megamonas*, *Erysipelatoclostridium*, *Dialister*, *Subdoligranulum*, *Holdemanella*, *Blautia*	[119]
Latino breastfed infants (n=103, Southern California, 6 months old); exposure to PM2.5	↓ *Alistipes*, *Proteobacteria*, *Rikenellaceae*; ↑ *Actinomyces*	[120]
Nrf2+/- rat (8-week-old); filtered vs. outdoor air (16h/day, 6 & 12 weeks)	↓ *Bacteroides*, *Firmicutes*, *Allobaculum*, *Prevotella*, *Sutterella*; ↑ *Alphaproteobacteria*, *Pseudomonadaceae*, *Desulfovibrionaceae*	[121]
Male C57BL/6 WT mice; exposed to PM2.5 for 5 months	↓ α-diversity; ↑ *Proteobacteria*; ↓ *Lactobacillus*, *Parabacteroides*, *Prevotella*, *Alloprevotella*, *Ruminococcus*, *Faecalibacterium*, *Bifidobacterium*	[111]
SD rats (6-8 weeks); oral gavage of PM2.5 (10 mg/kg/day for 28 days)	↓ *Firmicutes*, *Ruminococcaceae*; ↑ *Lactobacillaceae*, *Clostridium*, *Ruminae*, *Atopobiaceae*, *Coriobacteriaceae_UCG_002*	[122]
Male C57BL/6J mice (3-week-old); exposed to PM2.5 (8, 16, 24 weeks)	↓ *Bacteroidetes*, ↑ *Proteobacteria*; ↑ *Clostridium*, *Akkermansia*, *Acetatifactor*	[108]
Male BALB/c mice (8-week-old); exposed to PM2.5 (8h/day, 6 days/week for 6 weeks)	↓ *Bacteroidetes/Firmicutes* ratio; ↑ *Lactobacillus*, *Clostridium*; ↓ *Bacteroides*, *Parabacteroides*. (Post-recovery dominance of *Oscillospira*)	[109]
Male SD rats (SPF grade); passive lung inhalation of PM2.5 (10-20 mg/kg)	↓ *Cyanobacteria*, *Bacteroidetes*, *Proteobacteria*; ↑ *Verrucomicrobia*, *Elusimicrobiota*, *Desulfobacterota*, *Patescibacteria*, *Firmicutes*	[123]

6. Effect on Neurological Diseases

6.1. Neurodegenerative Disorders

Neurodegenerative diseases (NDDs) are defined by the progressive attrition of neuronal populations, culminating in debilitating cognitive or motor impairments. Central to the pathogenesis of these disorders is the MGBA, a bidirectional communication network that integrates the resident enteric microbiota with the CNS.

6.1.1. Alzheimer's Disease (AD)

Alzheimer's disease (AD), the primary cause of dementia globally, is defined by the extracellular accumulation of amyloid-β (Aβ) plaques, intracellular neurofibrillary tau tangles, and a progressive decline in cognitive function. Recent metagenomic analyses have consistently demonstrated that the AD gut microbiome is significantly distinct from that of age-matched, cognitively unimpaired cohorts. A hallmark of this dysbiosis is the marked depletion of anti-inflammatory genera, such as *Faecalibacterium* and *Eubacterium rectale*, coupled with the enrichment of pro-inflammatory or opportunistic taxa, specifically *Escherichia/Shigella* [124]. Clinical investigations have revealed that cognitively impaired individuals with confirmed brain amyloidosis exhibit an overabundance of *Escherichia/Shigella* and a deficit in *E. rectale*. Crucially, these taxonomic perturbations correlate with elevated levels of peripheral pro-inflammatory cytokines, suggesting a systemic link between enteric dysbiosis and neuro-inflammatory progression [125,126].

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6.1.2. Parkinson's Disease (PD)

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder characterized by the selective attrition of dopaminergic neurons in the substantia nigra and the systemic accumulation of α-synuclein aggregates. Gastrointestinal (GI) dysfunction represents a hallmark prodromal feature of PD, with up to 80% of patients manifesting chronic constipation and enteric motility issues years prior to the onset of motor deficits. Recent metagenomic characterizations have consistently identified significant dysbiosis in PD cohorts relative to neurologically normative controls. Specifically, the *Prevotellaceae* family notably the *Prevotella* genus, which is instrumental in butyrate biosynthesis and mucosal homeostasis is markedly depleted in PD patients [127]. *Prevotella* also contribute in mucin synthesis in gut which in turn maintain barrier integrity and immune regulation. The mucin-degrading bacterium *Akkermansia muciniphila* is frequently enriched in PD faecal profiles [128]. While *Akkermansia* is typically associated with metabolic health, its overabundance in PD may indicate a maladaptive shift toward excessive mucin degradation, potentially compromising the structural integrity of the intestinal barrier [129].

6.2. Neuroinflammation and Autoimmune Disorders

Neuroinflammation is characterized by an orchestrated inflammatory response arising from the dysregulated synthesis and secretion of pro- and anti-inflammatory cytokines within the CNS. Recent evidence identifies intestinal dysbiosis as a primary driver of neuroinflammation through the modulation of systemic inflammatory mediators. Specifically, a reduction in microbially-derived SCFAs attenuates their native anti-inflammatory signalling. This microbiome dysbiosis compromises the intestinal barrier, facilitating the translocation of pathogen-associated molecular patterns (PAMPs), such as LPS.

6.2.1. Multiple Sclerosis (MS)

Multiple sclerosis (MS) is an immune-mediated neuroinflammatory disorder defined by autoreactive inflammation, the demyelination of CNS axons, and subsequent neurodegeneration. Mounting evidence identifies significant enteric dysbiosis in MS patients, characterized by a marked reduction in butyrate-producing taxa such as *Faecalibacterium prausnitzii* and *Butyricicoccus*. These microbial deficits are typically accompanied by the enrichment of pro-inflammatory or mucin-degrading species, including *Akkermansia muciniphila*, *Prevotella* spp., *Methanobrevibacter*, and *Eggerthella* [130]. Under physiological conditions, butyrate serves as a critical signalling molecule for the induction and maintenance of regulatory T cells (Tregs). However, the overabundance of *Akkermansia* and *Ruminococcus* in MS cohorts which facilitates the erosion of the protective mucosal barrier—correlates with the expansion of pro-inflammatory Th17 cells within the intestinal mucosa, thereby driving systemic autoimmune activity [131].

6.2.2. Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS) is a rapidly progressive and fatal neurodegenerative disorder characterized by the selective attrition of motor neurons, culminating in muscular atrophy and paralysis. Clinically, ALS is frequently associated with a hypermetabolic state and gastrointestinal (GI) dysfunction, such as significant weight loss, which may enter into a bidirectional relationship with the enteric microbiota. In a pilot clinical trial, ALS patients adhering to a hypercaloric dietary regimen exhibited a significantly attenuated rate of functional decline compared to those on a normative caloric intake. This dietary shift is often associated with the enrichment of *Akkermansia muciniphila*, a taxa that thrives on mucin substrates under conditions of high lipid and low fibre intake. Notably, *Akkermansia* may exert neuroprotective effects by synthesizing bioactive metabolites such as nicotinamide [132]. These findings suggest that the gut microbiota can modulate the trajectory of neurodegeneration in ALS through the enhancement of specific microbial metabolic functions, including the biosynthesis of essential vitamins and cofactors.

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6.3. Neuropsychiatric Disorders

6.3.1. Major Depressive Disorder (MDD)

Major Depressive Disorder (MDD) is a multifaceted psychiatric condition primarily characterized by persistent anhedonia, psychomotor retardation, and cognitive impairment. Metagenomic characterizations of the MDD gut microbiome reveal significant taxonomic perturbations, most notably an enrichment of *Eggerthella* (Actinobacteria), *Subdoligranulum*, and *Coprococcus* (Lachnospiraceae), alongside a concomitant depletion of SCFA producing taxa within the *Ruminococcaceae* family. This dysbiotic profile is particularly acute in the inflammatory MDD subtype, which is characterized by an expansion of the *Bacteroidetes* phylum and a reduction in the *Clostridiales* order. Notably, the *Sellimonas* genus exhibits a dose-dependent positive correlation with clinical severity, potentially exerting its pro-inflammatory effects through the activation of the canonical TLR4/NF-κB pathway [133].

6.3.2. Schizophrenia

Schizophrenia is a multifaceted neuropsychiatric syndrome characterized by a complex constellation of cognitive, emotional, and occupational impairments. Emerging evidence suggests that intestinal barrier dysfunction, systemic bacterial translocation, and gastrointestinal comorbidities are significantly more prevalent in schizophrenic cohorts than in the general population. The pathophysiology of the disorder is increasingly linked to enteric dysbiosis and the aberrant shunting of the tryptophan-kynurenine metabolic pathway [134]. Specifically, taxonomic enrichment of the genera *Lactobacillus* and *Prevotella* has been identified in ultra-high-risk (UHR) patients. Enteric dysbiosis appears to exacerbate systemic inflammation by compromising intestinal barrier integrity—a process intricately linked to the dysregulation of the kynurenine pathway.

6.3.3. Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by repetitive behavioural patterns and significant deficits in social and linguistic communication. Clinically, ASD is frequently comorbid with diverse pathologies, including mood disorders, epilepsy, and gastrointestinal (GI) dysbiosis. The aetiology of ASD is increasingly linked to a homeostatic imbalance between pro-inflammatory *Clostridium* species and anti-inflammatory *Bifidobacterium* spp. [135]. Notably, the dietary intake of propionic acid or its metabolic precursors is correlated with exacerbated autistic behaviours and GI symptomatology.

6.3.4. Bipolar Disorder (BD)

Bipolar disorder (BD) is a chronic, recurrent affective disorder that shares significant symptomatic overlap with schizophrenia. It is clinically defined by pathological oscillations between depressive episodes and manic phases. Metagenomic characterizations indicate that individuals with BD exhibit a four-fold reduction in the *Clostridiaceae* family compared to healthy controls [136]. Furthermore, taxonomic stratification reveals that the class *Coriobacteriia* is significantly enriched in BD cohorts, whereas butyrate-producing taxa such as *Ruminococcaceae* and *Faecalibacterium* are markedly more abundant in normative controls, suggesting a loss of anti-inflammatory microbial support in the disorder [137].

6.4. Other Neurological Disorders

6.4.1. Epilepsy

Epilepsy is a neurological disorder defined by a predisposition to unprovoked, spontaneous seizures, primarily arising from a homeostatic imbalance between neuronal excitation and inhibition. Comparative metagenomic analysis of patients with drug-resistant epilepsy versus those responsive

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to therapy has revealed distinct microbial signatures. Notably, the gut microbiota composition of drug-responsive individuals appears comparable to that of healthy controls, suggesting a preservation of microbial homeostasis. Furthermore, a higher prevalence of *Bifidobacterium* and *Lactobacillus* has been correlated with lower seizure frequency (four or fewer annual episodes). Conversely, patients with drug-resistant epilepsy exhibit significantly elevated alpha-diversity indices, indicating that increased microbial richness in this context may be associated with refractory clinical outcomes [138].

6.4.2. Migraine

Migraine is a debilitating neurovascular disorder characterized by recurrent paroxysms of severe cephalalgia, frequently accompanied by autonomic symptoms such as nausea, emesis, and heightened sensitivity to multimodal sensory stimuli. The precise mechanisms governing the microbiota-gut-brain axis in migraineurs remain to be fully elucidated; however, current evidence suggests a multifactorial interplay involving pro-inflammatory cytokines (IL-1β, IL-6, IL-8, and TNF-α), distinct microbial profiles, and the dysregulation of neuropeptide and serotonergic signalling [139]. Glutamate, the primary excitatory neurotransmitter, is fundamentally implicated in migraine pathogenesis by facilitating cortical spreading depression (CSD), mediating central sensitization, and activating the trigeminovascular system.

6.4.3. Restless Leg Syndrome (RLS)

Restless Legs Syndrome (RLS), also clinically recognized as Willis-Ekbom Disease, is a sensorimotor neurological disorder characterized by an imperative urge to move the lower extremities. Differential abundance analysis has identified a statistically significant depletion of the *Lachnoclostridium* and *Flavonifractor* genera in RLS cohorts compared to both healthy controls (HC) and insomnia (INS) patient groups. Furthermore, a marked decrease in the relative abundance of four additional genera—*Bacteroides*, *Eisenbergiella*, *Blautia*, and *Dorea*—was observed in RLS patients relative to healthy controls, suggesting a distinct microbial deficit specific to the RLS enteric landscape [140].

6.4.4. Substance Use Disorder

Substance use disorders (SUDs) are characterized by persistent, maladaptive dependence and a profound inability to regulate consumption despite escalating biopsychosocial consequences. These disorders are underpinned by chronic neuroplastic alterations within central circuits governing executive function, stress reactivity, and reward processing. Vulnerability to such addiction-related phenotypes is a multifactorial byproduct of genetic predisposition, developmental stage, and adverse social determinants of health [141]. The gut-brain axis serves as a bidirectional biochemical conduit, where metabolic signals from the enteric microbiota influence CNS homeostasis and behaviour. Gut commensals are pivotal in the biosynthesis of neuroactive metabolites, including SCFAs and primary neurotransmitters like serotonin and dopamine. Addictive substances (e.g., alcohol, opioids, and/or other drugs) exploit the brain's dopaminergic reward pathway, precipitating a supraphysiological release of dopamine that drives repetitive consumption. Emerging evidence suggests that gut microbes modulate reward perception for both natural and pharmacological stimuli. Pathologically, SUDs are frequently associated with intestinal barrier dysfunction ("leaky gut"), which facilitates the systemic translocation of microbial products. This triggers a peripheral pro-inflammatory cascade; subsequent cytokine infiltration across the BBB induces neuroinflammation, thereby altering neuronal excitability within the reward circuitry and modulating substance tolerance and cravings [142,143].

Alcohol consumption exerts a direct, deleterious impact on intestinal micro-ecology. Both murine and clinical investigations demonstrate that alcohol induces significant shifts in microbial diversity and taxonomic composition. Patients with Alcohol Use Disorder (AUD) exhibit a distinct

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microbial signature characterized by a contraction of *Akkermansia* and an expansion of *Bacteroides* which serves as a diagnostic biomarker with 93.4% accuracy. This dysbiosis is associated with a systemic pro-inflammatory state, evidenced by significantly elevated serum lipopolysaccharide (LPS) and cytokines (TNF-α, IL-1, IL-6) [144]. The relationship between AUD and psychiatric comorbidities, such as depression and anxiety, is inherently bidirectional: pre-existing affective disorders increase the risk of alcohol abuse, while chronic alcohol exposure exacerbates neuropsychiatric symptoms [145]. The mechanistic link is further elucidated by faecal microbiota transplantation (FMT) studies. In a landmark study, mice receiving FMT from AUD donors who presented with high depression scores and depleted *F. prausnitzii* and *A. muciniphila* displayed impaired social behaviour, depressive-like endophenotypes, and hyper-cortisolemia. Intriguingly, the significant post-FMT enrichment of *A. muciniphila* in these mice suggests a complex, non-linear interaction between microbial consortia and the neurobehavioral axis, potentially involving species-specific synergies or host-specific metabolic responses [146].

Investigations into the interplay between opioid use disorders and the intestinal microbiome are rapidly expanding. In a comparative study involving 45 polysubstance abusers characterized by daily alcohol and nicotine consumption alongside heroin, methamphetamine (MA), or ephedrine, significant taxonomic shifts were observed relative to 48 healthy controls. Notably, the patient cohort exhibited a paradoxical increase in microbial diversity indices. Genus-level stratification revealed a distinct enrichment of *Prevotella*, *Paracoccus*, and *Thauera*, contrasted by a marked contraction of the *Bacteroides* phylum [147].

7. Conclusion and Future Directions

The evidence reviewed herein systematically challenges the traditional assumption that modern industrial xenobiotics function as isolated, organ-specific hazards. Instead, Particulate Matter (PM2.5), Microplastics (MPs), Inorganic Nanoparticles (NPs), and Non-Nutritive Sweeteners (NNS) converge to act as potent, synergistic disruptors of the MGBA. While each stressor initiates toxicity via distinct mechanisms—whether it be the epigenetic reprogramming induced by NPs [91], the mucosal abrasion and "plastisphere" pathogenic vectoring of MPs [62], the bacteriostatic shifts driven by NNS [40], or the mucociliary-to-gut translocation of inflammatory PM2.5 [107] they ultimately share a highly conserved, cascading pathological trajectory:

1. **Profound Dysbiosis:** A consistent depletion of neuroprotective, SCFA-producing taxa (e.g., *Faecalibacterium*, *Lachnospiraceae*) and the aberrant proliferation of opportunistic pathobionts (e.g., *Enterobacteriaceae*, *Proteobacteria*). This sharply diminishes the bioavailability of essential neuroactive mediators, including butyrate, GABA, serotonin, and indole derivatives.
2. **Barrier Disruption & Systemic Translocation:** The physical, chemical, and oxidative (ROS) erosion of critical tight junction proteins (ZO-1, Occludin) precipitates a "leaky gut" phenotype [89]. This facilitates the unrestricted systemic translocation of neurotoxic microbial products, such as lipopolysaccharides (LPS).
3. **Systemic Immune Dysregulation:** The disruption of mucosal homeostasis drives a peripheral pro-inflammatory cascade, characterized by elevated TMAO and the critical destabilization of peripheral immune tolerance (e.g., Treg/Th17 imbalance) that propagates via the gut-liver and gut-heart axes [64,69].
4. **Neurodegeneration:** The culmination of systemic inflammation and, in the case of nanoparticles and microplastics, direct xenobiotic translocation across the blood-brain barrier [70], triggers microglial activation, attenuates autophagic flux, and accelerates the aggregation of neurotoxic proteins (e.g., amyloid-β and p-Tau).

7.1. A Potential "Dual-Hit" Mechanism

Beyond the synergistic 'cocktail effect' of multiple xenobiotics, the reviewed evidence suggests a potential "dual-hit" scenario: modern industrial xenobiotics likely aggravate neurological

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pathology through simultaneous, compounding mechanisms. The first hit (Hit-1) is direct neurotoxicity: xenobiotics (such as nanoparticles and microplastics) physically translocate into the CNS via systemic circulation or olfactory routes, acting as immediate neurotoxicants that induce localized cellular damage. The second hit (Hit-2) is indirect: these same agents concurrently perturb the gut-brain axis from the "bottom up" through mucosal damage, dysbiosis, and chronic endotoxemia. The resulting gut-derived systemic inflammatory storm reaches the brain and severely exacerbates the direct toxic effects of Hit-1. This bidirectional assault—where the brain is targeted from both the systemic circulation and the enteric nervous system—may explain the accelerated trajectory of cognitive decline and affective disorders observed in highly industrialized populations.

7.2. The Therapeutic Paradox and Environmental Complexity

As nanotechnology rapidly advances, NPs are increasingly utilized as antimicrobial agents and targeted drug delivery systems. However, this review urges extreme caution: the specific physicochemical properties that facilitate their therapeutic translocation into the CNS may inadvertently induce off-target enteric dysbiosis and long-term neurotoxicity [148]. Furthermore, a critical disconnect exists between pristine laboratory toxicology and environmental reality. From a prospective vantage point, the industrial and biomedical utilization of NPs is projected to increase exponentially, leading to inevitable environmental bioaccumulation. A sobering historical parallel must be drawn with plastics: macro-plastics discarded half a century ago have insidiously degraded into the pervasive, bio-reactive microplastics currently disrupting environment and human health [149]. Similarly, the continuous accumulation and environmental weathering of today's nanoparticles may precipitate unforeseen, multigenerational ecological and physiological crises. Current safety assessments must evolve to account for the "eco-corona" the complex layer of biomolecules and concurrent pollutants that adsorb onto xenobiotics in real-world environments, dramatically altering their bioavailability and toxicity [150,151].

7.3. Future Directions:

To effectively mitigate the neurological burden of the modern industrial exposome, future research must prioritize four strategic domains:

1. **Addressing the "Cocktail Effect":** Real-world exposure is cumulative. Longitudinal human studies and advanced in vivo modelling must evaluate the synergistic toxicity of simultaneous exposure to microplastics, nanoparticles, air pollution, and non-nutritive sweeteners on neuro-metabolic markers.
2. **Broadening the Neurological Scope:** There is a critical need to expand investigations beyond classical neurodegeneration (AD/PD) to elucidate the causal correlations between modern xenobiotics and underexplored pathologies, including migraine, epilepsy, restless leg syndrome, and the alarming escalation of substance use disorders.
3. **Safe-by-Design Nanomedicine:** The development of future oral therapeutics and food packaging must prioritize rigorous preclinical screening to filter out nanomaterials that inadvertently trigger mucosal oxidative stress or downregulate tight junction proteins.
4. **Targeted Microbiome Interventions:** Therapeutic strategies must pivot towards rescuing the MGBA through "psychobiotics" and targeted postbiotics. Exploring the therapeutic administration of specific neuroprotective metabolites (e.g., SCFAs, Indole Propionic Acid) or bio-engineering probiotic consortia capable of degrading the MP "plastisphere" offers a promising frontier for preserving long-term neurological resilience against environmental disruptors.

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