microplastics

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Review

Plastamination in Human Brain: The Possible Role of Microplastics in Neuroinflammation and Parkinson's Disease

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Abstract

Plastic contamination (plastamination) has become a pervasive environmental threat with growing implications for human health. Among plastic-derived contaminants, micro- and nano-plastics (MNPs) are of particular concern due to their persistence, widespread distribution, and capacity to interact with biological systems. Humans are exposed to MNPs through ingestion, inhalation, dermal contact, and maternal transfer, and these particles can cross biological barriers, including the blood–brain barrier, reaching the central nervous system. MNPs disrupt cellular homeostasis by inducing oxidative stress, mitochondrial dysfunction, and inflammation. In the brain, these processes drive glial activation and chronic neuroinflammation, which are closely associated with neuronal damage and neurological disorders, including Parkinson's disease (PD). MNPs can also affect systemic pathways such as the gut–brain axis (GBA) and neuroendocrine regulation, suggesting broader physiological consequences. This narrative review synthesizes current evidence on the neurotoxic and pro-inflammatory potential of MNPs. Since MNPs may promote the aggregation of proteins implicated in neurodegeneration, such as alpha-synuclein, their possible role in PD is discussed. Despite several knowledge gaps, MNPs may be emerging environmental risk factors for brain health and neurodegenerative diseases such as PD. Nevertheless, there is a need for further studies in the field, standardized methodologies and longitudinal studies to implement effective mitigation strategies.

Keywords: microplastics; nanoplastics; neuroinflammation; blood–brain barrier; α-synuclein; Parkinson's disease

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1. Introduction

Environmental plastic contamination (here referred to as "plastamination" from the fusion of the words *plast*ic and cont*amination*) has emerged as a global environmental issue with increasingly recognized implications for human health [1]. Although plastics have positively changed our lives since the 1950s, their large use and incorrect disposal have caused

their accumulation in the biosphere and made them a real threat, and a global environmental and health emergency. The worldwide production of plastic reached 430.9 million metric tons in 2024, having increased at a compound annual growth rate of 4.8 percent since 2009. Annual production volumes are expected to continue rising in the following decades, reaching approximately 590 million metric tons by 2050. In parallel, global plastic waste volume reached around 6.3 billion metric tons in 2015, and it is expected to increase to 12 billion metric tons by 2050 [2,3].

Currently, among plastic-derived contaminants, microplastics (MPs, <5 mm) and nanoplastics (NPs, <1 μm) have gained particular attention due to their persistence, widespread distribution, and capacity to interact with biological systems [4,5]. They are water-insoluble solid polymers that differ by size, shape, and surface reactivity; they originate mainly from anthropogenic activities and derive from both primary and secondary sources. Primary MPs are intentionally manufactured for specific applications, including personal care products, medical, and industrial uses, whereas secondary MPs result from the environmental fragmentation of larger plastic items due to physical, chemical, and biological processes [6]. Major sources include synthetic textiles, tire wear, marine coatings, road markings, plastic packaging, personal care products, and urban dust. Heat exposure during food preparation or storage, such as microwave or oven use, can further promote the release of MPs and NPs from plastic containers and packaging materials [7,8].

Usually, environmental plastamination consists of a mixture of various types of plastics. In general, petroleum-based plastics, also known as conventional plastics, are polymers derived from fossil fuels, either gas or crude oil, thus resulting non-biodegradability in the environment. They include polyethylene (PE), polypropylene (PP), polystyrene (PS), polyvinyl chloride (PVC), and polyethylene terephthalate (PET) [2]. PE and PP alone are responsible for over 50% of the world's plastic production, thus representing the largest and leading industrial volume polymers, with large use as packaging materials [3]. Conventional plastics also include biodegradable polymers (e.g., polybutylene adipate terephthalate (PBAT), polycaprolactone (PLC) and polybutylene succinate (PBS)). They have been designed to biodegrade under certain conditions and in varying periods of time.

Non-conventional plastics or "green plastics" include bio-based plastics derived from renewable products such as carbohydrates, starch, vegetable fats and oils, bacteria and other biological substances; they can be biodegradable (e.g., PHA, polyhydroxyalkanoates; PHB, polyhydroxybutyrate; PLA, polylactic acid; PLGA, polylactic-co-glycolic acid A) or non -biodegradable (e.g., bio-PET, bio-PP, bio-PE). Furthermore, the production of plastics usually requires the use of additives or plasticizers (e.g., bisphenol A (BPA), flame retardants (PBDEs), phthalates, stabilizers, colorants) to gain specific properties; most plastic additives deeply interfere with human physiology, acting as recognized endocrine disruptors [9–12]. In addition, due to their chemical properties, MPs and NPs (collectively named MNPs) can concentrate persistent organic pollutants, heavy metals, or microorganisms on their surface. Through this "Trojan horse" effect, MNPs act as vehicles to deliver co-contaminants into biological systems, amplifying toxicity attributable to either particles or chemicals alone [13,14]. For example, PS-MNPs can serve as a vehicle for pathogenic biofilms that significantly exacerbate neurotoxic effects on fully differentiated human cortical neurons [15]. Similarly, PS-MPs exhibit strong adsorption capacity for thallium, and in *Caenorhabditis elegans*, PS-MP/thallium co-exposure induces more severe neuronal damage and neurotransmitter disruption than individual pollutants [16].

MPs enter the food chain and have been found in both tap and bottled water, partially coming from the packaging and/or the bottling process itself [17,18]; fragments of PE, PP, and PS are among the top three polymer types found in water samples [19]. Humans are exposed to MNPs through multiple routes, including ingestion of contaminated food and

water, inhalation, dermal contact, placental transfer and breast milk [20–22]. Hence, these particles can translocate across biological barriers (e.g., gut epithelium barrier, placental barrier, blood–brain barrier (BBB), and blood–testis barrier (BTB)), enter systemic circulation, and accumulate in peripheral organs and tissues [13,14]. Following their uptake in cells and tissues, MNPs induce oxidative stress, inflammation, apoptosis, immune response activation and other toxicological pathways [23,24].

Experimental data indicates that MNPs, due to their small size and surface properties, can cross the BBB and access the central nervous system (CNS) via both hematogenous routes and neural pathways such as the olfactory system and the gut–brain axis (GBA) [13,14,23]. These effects converge on glial activation and sustained neuroinflammatory responses, characterized by microglial and astrocytic reactivity and increased release of pro-inflammatory mediators [25–27].

In this respect, Parkinson's disease (PD), a progressive neurodegenerative disorder affecting 1–2% of people over age 65 and marked by dopaminergic neuron loss and α-synuclein (α-syn) aggregation [28–30], is increasingly recognized as a multifactorial condition arising from the interaction between genetic susceptibility and environmental factors [31,32]. While pesticides, metals, and industrial chemicals have long been recognized as environmental risk factors [33,34], it has recently been proposed that MNPs are emerging contributors to PD-related pathology [35–37]. Experimental studies suggest that these particles can promote α-syn aggregation, impair proteostasis mechanisms, and amplify neuroinflammatory signaling, thereby potentially exacerbating pathways central to PD progression [35,38].

Hence, in this narrative review, we provide an integrated overview of current knowledge on MNPs as emerging environmental risk factors for brain health, with a specific focus on PD and the potential contribution of NMPs to PD pathology through neurotoxic and neuroinflammatory mechanisms. Figure 1 summarizes the main features of MNPs and the consequences of MNP exposure in the brain.

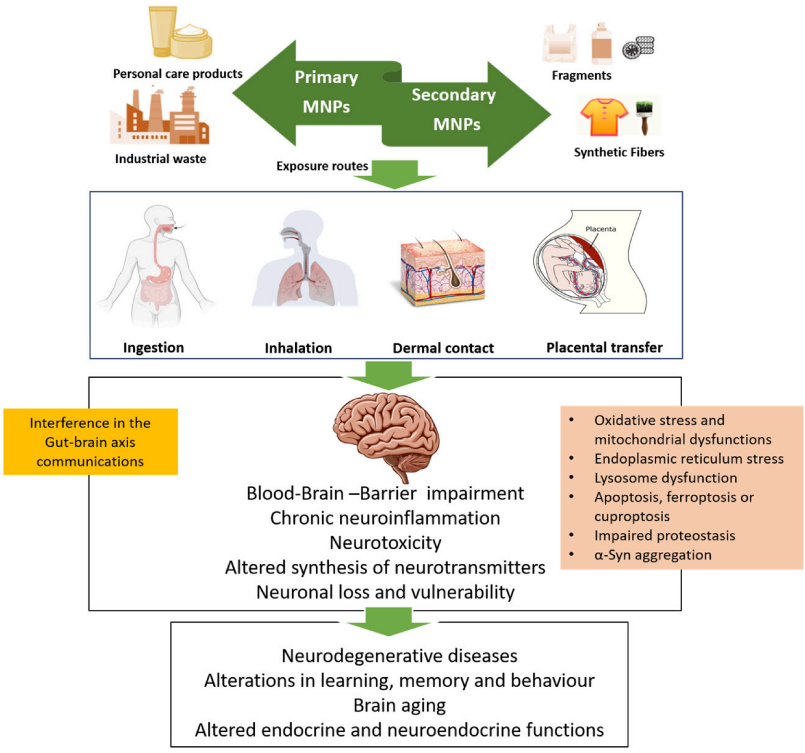

Figure 1. Sources, exposure pathways, and potential neurotoxic effects of MNPs. MNPs can originate as primary particles or as secondary particles generated through the fragmentation and degradation

of larger plastics. Major sources of MNPs include synthetic fibers, personal care products, industrial waste, and plastic fragments. Human exposure may occur through multiple routes, including ingestion, inhalation, dermal contact, and placental transfer. Following exposure and potential systemic distribution, MNPs exert adverse effects on the central nervous system, impairing the blood–brain barrier, promoting chronic neuroinflammation, neuronal loss and increased neuronal vulnerability. At the cellular level, oxidative stress and dysfunctions in the mitochondria, endoplasmic reticulum and lysosomes occur. α-Synuclein aggregation also occurs in dopaminergic neurons. These alterations may contribute to neuronal dysfunction and the pathophysiological processes associated with neurodegenerative diseases, including Parkinson's disease.

2. MNP-Driven Inflammatory Processes

Neuroinflammation, the inflammatory process occurring within the brain in response to infections, injuries or trauma, involves the activation of glial cells, mainly astrocytes and microglia, and the release of pro-inflammatory mediators as well [39] (Figure 2).

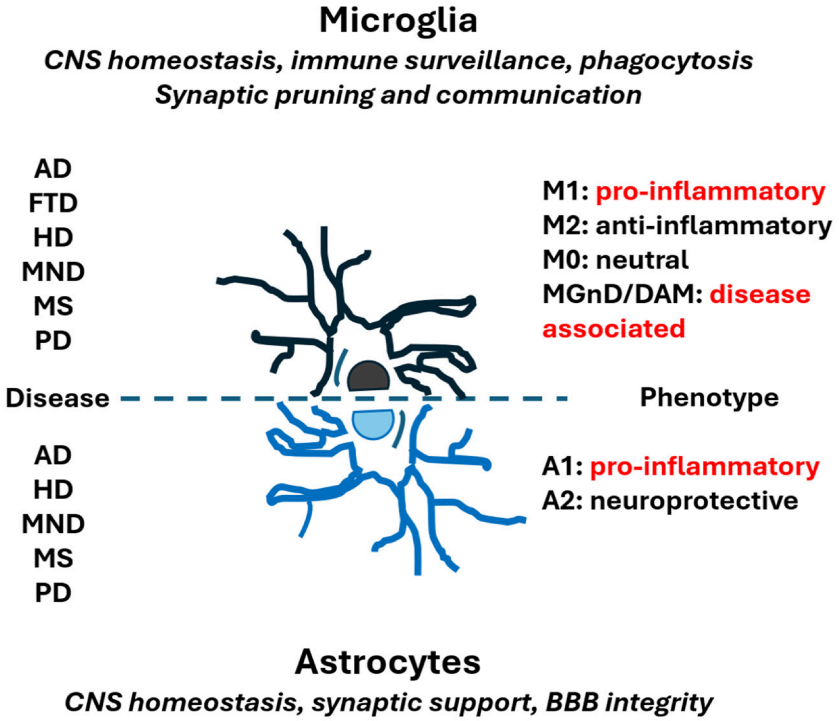

Figure 2. Microglia vs. astrocytes in health and disease. Schematic overview of microglia and astrocytes in physiological conditions and in neurological diseases (red phenotype, on the right). Pathological conditions related to microglia/astrocyte activation are on the left. AD, Alzheimer's disease; FTD, frontal–temporal lobe dementia; HD, Huntington's disease; MGnD/DAM, neurodegenerative microglia/disease-associated microglia; MND, motor neuron disease; MS, multiple sclerosis; PD, Parkinson's disease.

In physiological conditions, glial cells provide trophic and structural support to neurons, making them essential for neuronal health. Nevertheless, when exacerbated, this protective inflammatory response can turn into a never-ending response that damages neuronal tissues, leading to neuronal loss, neurodegeneration and the development of neurological disorders such as PD, Alzheimer's disease (AD) or multiple sclerosis (MS), among others [40–44] (Figure 2).

Hence, the main consequences of microglia activation (i.e., astrogliosis) are the production of inflammatory mediators and reactive oxygen species (ROS) and changes in the homeostasis of the BBB [45,46], the selective barrier that protects the brain from harmful substances while allowing essential nutrients to pass through.

An early and key event in MNP toxicity is the development of oxidative stress and inflammation [47]. Many studies have shown a consistent rise in ROS levels after exposure to these particles [48,49]. ROS can directly damage cellular components such as lipids, proteins, and DNA; they also trigger the activation of pro-inflammatory pathways. Usually, oxidative stress is a result of ROS production and the reduction of endogenous antioxidant enzymatic machinery. For example, low-density PE-MPs (<30 µm) significantly compromised the BBB in male rats after both 3 and 6 weeks of exposure, leading to a decrease in superoxide dismutase (SOD) levels and an increase in malondialdehyde (MDA). In parallel, decreased levels of brain-derived neurotrophic factor (BDNF) and neuronal damage were also observed [50]. Consistently, suppressed oxidative stress markers (i.e., the scavenging antioxidant glutathione (GSH), the antioxidant enzymes SOD and the transcription factor nuclear factor erythroid 2-related factor (Nrf2) which regulates the expression of genes involved in the antioxidant response and in protecting cells against free radicals and other reactive oxygen molecules), alongside activation of the ERK-MAPK pathway, ultimately resulting in deficits in learning and memory due to cuproptosis, have been observed in a mouse model treated for 30 days with PS-NPs (60 nm, 12.5 mg/kg by gavage) [51]. Supporting the role of oxidative stress in cell damage, combined treatments with antioxidants such as N-acetylcysteine or glutathione significantly reduce NP toxicity in differentiated THP-1 macrophages, in neuronal cell lines, in the fetal brain and in mouse models, highlighting the causal role of oxidative stress [51–53].

MNP-exposure-dependent oxidative stress leads to the activation of the innate immune response, characterized by the release of pro-inflammatory cytokines. Among these, interleukin-1β (IL-1β), IL-6, and IL-8 are those whose increase has been most frequently and consistently observed in cell lines (e.g., human lung epithelial BEAS-2B cells) and in in vivo treated mice [54–57]. These cytokines are classic players in the acute inflammatory response: IL-1β promotes fever and endothelial activation, IL-6 stimulates the hepatic synthesis of acute-phase proteins, and IL-8 acts as a potent chemokine, recruiting neutrophils to the inflammation site [58]. Another key cytokine is tumor necrosis factor-alpha (TNF-α) [59], a pleiotropic mediator of inflammation involved in endothelial activation, cell migration, and apoptosis; its overexpression is a clear indicator of an ongoing immune response [60]. Increased secretion of IL-6 and TNF-α is dependent on PS-MP dose and size in peripheral blood mononuclear cells (PBMCs), with PS particles less than 3 µm in diameter at a concentration of 500 µg/mL being effective on IL-6, while a high concentration (500 µg/mL) of 0,46 µm PS particles is only effective on TNF-α [61]. Similarly, significant enrichment of IL-6, TNF-α and other inflammatory factors has been reported in the testes of mice treated for 28 days by gavage with 10 mg/mL PS-MP beads of 0.5, 4, and 10 µm diameter [62]. The persistence of this inflammatory stimulus can lead to tissue damage and the chronicity of the process. A critical mechanism in this step is the impairment of epithelial barrier integrity, such as in the intestinal or pulmonary barriers. Studies have shown that MNP exposure reduces transepithelial resistance and the expression of tight junction proteins, such as zonula occludens 1 (ZO-1) [62]. This loss of cellular barrier integrity allows an uncontrolled passage of substances and potentiates local inflammation. NPs can even be internalized by cells through membrane vesicles, amplifying damage from within [63]. Clinically, this mechanism underlies the association between MNP exposure and pathologies such as chronic obstructive pulmonary disease (COPD), asthma [64], and inflammatory bowel diseases (IBD) [48,65,66].

In addition to these well-established mediators, the role of other molecules has been investigated. For example, an increase in the chemokine MIP1β following exposure to fresh and weathered PP-MPs and PS-MPs has been reported in THP-1 macrophages [52]. Considering that MIP1β is an important chemotactic factor produced by macrophages

and monocytes in response to inflammatory stimuli [67], this finding opens interesting perspectives, although it requires confirmation. Similarly, the possible involvement of cytokines such as interferon-gamma (IFN-γ), crucial for macrophage activation [68], and growth factors like G-CSF (involved in granulocyte production during the acute phase) and FGF-8 (implicated in fibroblast proliferation and chronic inflammation) [69], suggests a broader spectrum of action for MNPs than is currently known [49].

3. Plastamination in the Brain

Recently, the exposome has been included as a possible threat to neuroinflammation, brain aging and neurological diseases in combination with genetic factors [27,70,71]. Therefore, MNPs have become a potential risk factor for the development and progression of neurodegenerative diseases [13,72–74], as highlighted in recent review articles. Currently, epidemiological and clinical data in humans are very limited; thus most studies have been carried out in vitro or in vivo. Nevertheless, experimental evidence in cell lines and animal models is sometimes conflicting, due to different concentrations of MNPs, types of plastic, or sizes that do not fully match the real environmental plastamination [13,72–74]. However, the main mediators and mechanisms by which MNPs interact with biological systems, triggering neuroinflammation and neurodegeneration, have begun to be identified. Therefore, in the next paragraphs, we summarize the main insights in the field.

3.1. Exposure Routes

The main exposure routes for MPs, NPs and plastic additives like bisphenols or phthalate are ingestion or inhalation; dermal contact and placental transfer must also be considered (Figure 1). Accordingly, MPs are detected in food products, water, and even the air [13,14]. Once internalized in the body, MNPs cross biological barriers such as the gut epithelium barrier, placental barrier, BBB, and BTB; enter systemic circulation; induce systemic inflammation and accumulate in peripheral organs [13,14] such as the brain [75], causing potential long-term effects on neuronal health [76,77].

First, MNPs are able to cross the BBB [78]. This barrier is overcome via clathrin- or caveolae-mediated endocytosis mechanisms [79,80], followed by transcytosis across the endothelial layer. Kopatz et al. [81] performed short-term uptake studies in mice with orally administered 100 µL PS-MNPs (9.55 µm, 1.14 µm, 0.293 µm), revealing that NPs—but not MPs—reach the brain within 2 h after gavage. Usually, in biological fluids, plastic particles can accumulate on their surface a layer of proteins and other biomolecules, called biomolecular corona [82]; similarly, in the environment, MNPs can acquire a large plethora of environmental "eco-coronae" consisting of different biomolecules, biological contaminants, or organic matter [83]. Interestingly, simulations of molecular dynamics using a 1,2-Dioleoyl-sn-glycero-3-phosphocholine (DOPC) bilayer revealed that the composition of the biomolecular corona on the surface of the plastic particles is critical for passage through this BBB model. Since cholesterol in the corona, but not proteins, enhanced the uptake of 5 nm PS-NPs into the membrane of the BBB, passive transport has been suggested [81].

Concurrently, different mechanisms involving junctional proteins have been suggested. In fact, nanoscale particles can compromise tight junction integrity by inducing oxidative stress and inflammatory responses, thereby increasing BBB permeability and allowing paracellular passage [84,85]. In hCMEC/D3, a recognized model of the BBB, PS-NPs with a nominal mean diameter of 42 nm cause ROS production, nuclear factor kappa-B (NF-κB) activation, TNF-α secretion, necroptosis and dysfunctions in the tight junction, suggesting neurotoxic effects via microglia activation [27]. Accordingly, BBB damage after CNS infection accelerates the accumulation of MNPs in the human cerebrospinal fluid

(CSF) [86], with PS, PE, PP, and PVC selectively capable of entering the human CNS [86]. A direct access route is represented by the olfactory nerve: inhaled particles deposit on the olfactory mucosa, are internalized by receptor neurons via endocytosis, and are transported to the olfactory bulb through axonal transport mechanisms [87,88].

Lastly, the gut communicates with the brain via the vagus nerve and through the systemic circulation of metabolites, hormones, and immune factors, forming the GBA. In this respect, the vagus nerve, conversely, offers an indirect pathway whereby MNPs introduced through the alimentary route interact with the intestinal epithelium, can be absorbed through Peyer's patches [89], migrate into the enteric nervous system, and ascend via vagal afferents to reach the brainstem and disseminate to higher brain regions [90,91].

Concerning dermal exposure, current data on MNP uptake by skin has been recently reviewed [92].

3.2. MNPs in the Brain: Molecular Mechanisms

Once in the brain parenchyma, MNPs trigger neuroinflammation. Particle accumulation in neural cells causes mechanical membrane damage with the release of danger-associated molecular patterns (DAMPs), which activate microglia, inducing the release of pro-inflammatory cytokines [93,94]. Simultaneously, ROS generation [95,96] induces oxidative stress, jeopardizing neurons and activating both microglia and astrocytes. Glial activation amplifies the inflammatory response, creating a vicious cycle of cellular damage [97,98]. In vitro studies have demonstrated that astrocytes exhibit high sensitivity to PS-MNP toxicity, with particle internalization and activation of inflammatory genes leading to astrogliosis [99]. In vivo studies have furthermore highlighted that PS-MNPs can occlude cerebral capillaries, reducing blood flow and inducing neuroinflammation from ischemic damage in turn [76].

At the molecular level, MNPs activate specific pro-inflammatory pathways, including the NF-kB pathway, leading to TNF-α and IL-6 secretion [100,101], and inflammasome formation, which stimulates IL-1β and IL-18 release [102,103]. At the cellular level, mitochondria are particularly vulnerable, contributing to metabolic deficit, ROS production, and apoptotic pathways.

In addition, epigenetic changes affecting both the nuclear and mitochondrial genomes have been recently reported and reviewed, in parallel to interference in the reciprocal network between mitochondria and the nucleus [104,105]. These modifications include changes in DNA methylation at CpG sites, histone modifications and dysregulation of non-coding RNA, such as microRNA [104,105]. Interestingly, circular mitochondrial DNA (mtDNA) lacks histone proteins and is more prone to oxidative stress damage under environmental stress. The displacement loop (D loop), the region critical for the replication of mtDNA and the transcription of mitochondrial genes, is the main target for mtDNA methylation [77]. Interestingly, the methylation levels within the D loop have been correlated with the pathogenesis of neurological diseases [106]. Recent observations in cell lines and animal models reported MP-dependent epigenetic effects in the brain. For example, in mouse hippocampal neuronal HT22 cells, silver NPs increased DNA methylation and elevated the levels of DNA methyltransferases DNMT1, DNMT3, and DNMT3A B [107]. A competing endogenous RNA (ceRNA) network containing 7 circRNAs, 19 miRNAs and 35 synaptic dysfunction-related mRNAs was constructed in mice following chronic PS-NPs exposure (25 nm, at 50 mg/kg doses by gavage for six months); this ceRNA has been related to impaired cognitive functions [108]. Although further investigation in the field is mandatory, these epigenetic signatures parallel the epigenetic changes reported in neuroinflammatory diseases, compromise neuronal integrity, propagate chronic neuroinflammation and oxida-

tive stress, and contribute to synaptic instability, persistent transcriptional reprogramming, and increased susceptibility to neurological diseases such as AD, PD, and ALS [104].

Contributing to neuroinflammation are also toxic additives present in plastics, such as BPA and phthalates, which act as endocrine disruptors [109–111], and neurotoxic substances like flame retardants and plasticizers, which can leach from particles and directly damage neuronal tissue [112,113].

The cumulative effect of the aforementioned mechanisms can establish a state that, over time, may contribute to the development and progression of neurodegenerative diseases such as AD and PD [114–119]. Consistent with this, a toxicity study by Liang and coworkers revealed that PS-NPs of 50 nm administered by gavage for 28 days at 0.25, 2.5, 25, and 250 mg/kg BW doses caused PD-like neurodegeneration in mice; single-nucleus transcriptomics analysis reported that PS-NPs caused energy metabolism disorders in the substantia nigra pars compacta (SNpc) and striatum [120].

3.3. Plastamination in the Brain: Biological Effects

The neurotoxic effects of MNPs have been investigated in animal models, with significant consequences on neurodevelopment, brain sexual differentiation, behavior and reproductive function, both directly on the exposed subjects and indirectly on their progeny through maternal–fetal transfer of MNPs and epigenetic mechanisms [11,13,71,76,121,122]. Mitochondrial dysfunction, chronic inflammation, disruption of calcium signaling and neurotransmission, altered lipid metabolism, and hormonal imbalance are the main features of in vivo MNP exposure [27,70,71]. For example, oral exposure to PS-MNs during pregnancy (1 mg/day during gestation) resulted in the accumulation of MNPs in the alimentary tract, brain, uterus, and placenta in maternal mice, as well as the infiltration of PS-NPs within the developing fetal thalamus. Consequently, the exposed progeny had anxiety-like behavior and a reduction in γ-aminobutyric acid (GABA) in the prefrontal cortex and amygdala [53]. Since gonadal differentiation and neuronal circuitry are both remodeled in fetal life, early life insults may affect neurobehavioral trajectories across generations. Nevertheless, antioxidant supplementation, both in vivo and in vitro, mitigated the deleterious effects of MP exposure on progeny behavior and neuronal cell lines [53]. Hence, the placenta represents a maternal-fetal interface that allows nanoscale particles to enter fetal circulation and accumulate in developing organs, leading to multiple adverse outcomes, such as fetal growth restriction, oxidative stress, inflammation, skeletal malformations, intestinal dysbiosis, endocrine disruption, altered gene expression in the brain [122] and sex-specific effects on the developing brain [123]. For example, the female brain is more susceptible than the male brain to hippocampal degeneration following oral exposure of dams to PP-NPs with a diameter of 500 nm (0.5 mg/day) during pregnancy and lactation [121]. This finding may be due to sex-specific consistent reductions in neuroprotective lipids, including lysophosphatidylethanolamines (LPEs) and plasmalogen.

In this respect, the hypothalamus is highly sensitive to plastics and plastic additives exerting endocrine-disrupting activity [9,11,13]. This brain area contains networks involved in the control of reproduction in both sexes and sexually dimorphic nuclei; it is highly responsive to environmental pollutants, particularly during pre-/post-natal brain development and sex maturation. Mechanistically, molecular and epigenetic modulation of well-known actors in the central control of reproduction (e.g., GnRH, Kiss1, estrogen receptors etc.) occurs [9].

Evidence from animal models, albeit indirect and based on the measurement of circulating gonadotropins or sex steroids, has supported the view that MNPs interfere with reproductive function through disruption of the HPG axis, suggesting that central endocrine disruption by MNPs may contribute to peripheral gonadal damage [13,111,124–127]. Only

recently has the direct impact of MNPs on the hypothalamus been reported in the control of the reproductive axis [128], thus shifting the focus from isolated gonadal toxicity toward a broader neuroendocrine framework that coordinates hypothalamic and pituitary pathways through gonadotropin releasing hormone (GnRH) secretion, downstream gonadotropin release and sex steroid homeostasis. In mammals, advanced puberty onset, with parallel activation of microglia, astrocytes and increased *GnRH* expression within the hypothalamus, has been reported in mice following PE- and PVC-MP exposure at doses of 3 mg/day and 6 mg/day respectively. Accordingly, circulating levels of MPs have been detected in girls affected by precocious puberty [128]. In vitro studies show that PS-NPs enter cells via non-classical endocytosis, affecting neuroendocrine function in GT1-7 cells and impairing migration in GN11 cells. Consistently, key genes linked to GnRH neuron development have been transcriptionally deregulated [129]. Hence, recent evidence suggests that MNPs act as endocrine and epigenetic disruptors and, through inflammation, oxidative stress, and epigenetic changes, reshape hypothalamic circuits governing reproduction and socioemotional behavior [122]. Beyond the hypothalamus, inflammation also drives MNP effects on the brain through the GBA. The potential neuroinflammatory consequences of GBA imbalance have been recently proposed and reviewed elsewhere [130]. Accordingly, MNP effects on the GBA have also been reported in nonmammalian and mammalian animal models [13] and in humans [130], with the development of gastrointestinal disorders, inflammation and chronic diseases [130]. In fact, MPs accumulate in the gastrointestinal tract and have been detected in adult stool and infant meconium [38,131], where they disrupt the gut microbiome and cause dysbiosis. Notably, elevated plastic levels have recently been reported in patients with Crohn's disease [132] pointing to a clinical association between plastic burden and intestinal inflammation.

Mechanistically, MNPs disrupt the GBA through a self-reinforcing sequence that ultimately converges on the brain. By reshaping the microbial community toward pro-inflammatory taxa and altering short-chain fatty acid (SCFA) signaling, MNPs compromise the intestinal epithelium, downregulating tight-junction proteins and increasing mucosal permeability, which allows plastic particles, bacterial lipopolysaccharide (LPS) and pro-inflammatory cytokines to reach the systemic circulation. This barrier failure and dysbiosis do not remain confined to the gut but propagate along multiple organ axes [133]. In the brain, these circulating mediators undermine BBB integrity and, either humorally or through vagal afferent signaling, prime microglia and sustain the central neuroinflammatory tone [99]. Two recent studies support this cascade at the mechanistic level. In a murine model, chronic oral exposure to PE and PP MPs disrupted intestinal barrier integrity and triggered parallel oxidative and inflammatory changes in both the gut and brain, with reduced ZO-1, increased lipid peroxidation (malondialdehyde, MDA) and elevated NF-κB-driven cytokines (TNF-α, IL-1β), thereby providing—via the NF-κB/PPAR-γ/BDNF axis—a direct molecular bridge between gut damage and central inflammatory and neurotrophic imbalance [134]. Importantly, this vulnerability is not restricted to conventional polymers. In mice, a 180-day dietary exposure to food-relevant doses of starch-based (biodegradable) MPs caused an overproduction of gut short-chain fatty acids (SCFAs). This SCFA overload, together with starch-derived nanoparticles detected in brain tissue, perturbed cerebral fatty acid homeostasis and provoked neuroinflammation, increasing Aβ-42 deposition and impairing learning and memory [135]. Also, in adolescent mice, exposure to 0.5 mg/day PS-MPs/NPs with diameters of 5 μm and 0.5 μm, respectively, severely impaired cognitive functions but with different mechanisms: PS-NPs caused neuron loss and inhibition of neurogenesis, while PS-MPs caused dendritic spine loss in the hippocampus. A multi-omics approach revealed neurotoxic mechanisms involving the

PI3K/AKT pathway and concomitant interference in the hippocampal metabolome and gut microbiota [136].

Lastly, the detection of MPs in a cohort of decedent brains with documented dementia diagnosis [137], the recovery of elevated blood MP levels in PD patients [138] and the detection of MNPs in the cerebrospinal fluid of amyloid-positive subjects [139] and patients with intracranial aneurysms [140] have provided new insights into neuroinflammation, disease-related neuronal vulnerability and MNP exposure. Details on the recovery of MNPs in blood, post-mortem human brain tissue and cerebrospinal fluid have been summarized in Table 1.

Table 1. Studies on the detection and quantitative concentration data of MNPs in blood and post-mortem human brain tissue and cerebrospinal fluid.

Author, Date	Human Biological Sample	Plastic Type	Sample Size	Plastic Size/ Concentration
Cui et al., 2025 [141]	Blood	PE (46.5%), PVC (16.8%), SBR (16.3%), PP (9.2%), PS (3.0%), ABS (2.2%), PET (1.7%), PMMA (1.3%), PC (1.1%), PA6 (0.9%), PU (0.5%), PA66 (0.4%)	*n* = 20	Not specified/ 12.1–303.2 µg/g
Huang et al., 2026 [142]	Blood	PE (72%), PS, PVC, PP	*n* = 36	Not specified/ Mean: 5.0 µg/mL
Lee et al., 2024 [143]	Blood	PS (58.3%), PP (50.0%), PE (38.9%), PET (16.7%), PA (8.3%)	*n* = 36	20–50 µm (most common)/ Mean: 4.2 MPs/mL
Leonard et al., 2024 [144]	Blood	PE (32%), EPDM (14%), EVA/EVOH (12%)	*n* = 20	Length: 7–3000 µm; width: 5–800 µm/ 1.84–4.65 µg/mL
Leslie et al., 2022 [145]	Blood	PET (50%), PS (36%), PE (23%), PMMA (5%)	*n* = 22	≥700 nm/ PE > 7.1 µg/mL; PS > 4.8 µg/mL; PET > 2.4 µg/mL
Xu et al., 2025 [138]	Blood	PVC, PP, PA66, PE, PS	*n* = 21 PD, 12 controls	Not specified/ PD: 21.36 ± 8.42 µg/g; Controls: 13.56 ± 5.92 µg/g
Amato-Lourenço et al., 2024 [87]	Olfactory bulb	PP (43.8%), PA (12.5%), Nylon (12.5%), PEVA (12.5%), PE (6.3%), Perlon PA (6.3%), Wool-PP (6.3%)	*n* = 15 (8 positive)	Particles: 5.5–26.4 µm; Fibers: 19.0–24.5 µm/ Not specified
Dzierżyński et al., 2025 [146]	Brain (white matter)	PET, PI, PLA	*n* = 1	Fibers: 230–1758 µm (length); 8–21 µm (width)/ 24.4 MPs/g
Nihart et al., 2025 [137]	Brain (frontal cortex)	PE (~75%), PP, PVC, SBR	*n* = 28 (2016), *n* = 24 (2024), *n* = 12 (dementia), *n* = 27 (East Coast)	100–200 nm/ 2016: 298.5–8861 µg/g; 2024: 2216–6791 µg/g; Dementia: 12,806–47,730 µg/g; East Coast: 74.7–2685 µg/g
Xie et al., 2024 [86]	Cerebrospinal fluid	PS, PE, PP, PVC	*n* = 28	<100 µm/ Not specified

Abbreviations: acrylonitrile butadiene styrene (ABS); ethylene propylene diene monomer (EPDM); ethylene vinyl acetate (EVA); ethylene vinyl alcohol (EVOH); microplastics (MPs); nylon (Nylon); polyamide (PA); polyamide 6 (PA6); polyamide 66 (PA66); polycarbonate (PC); polyethylene (PE); polyethylene terephthalate (PET); polyethylene vinyl acetate (PEVA); polyimide (PI); polylactic acid (PLA); polymethyl methacrylate (PMMA); polypropylene (PP); polystyrene (PS); polyurethane (PU); polyvinyl chloride (PVC); styrene–butadiene rubber (SBR); wool–polypropylene (Wool-PP).

Taken together, MNPs deeply affect brain physiology, posing conditions for brain diseases, as well as neurodevelopmental, cognitive, behavioral and reproductive dysfunction, with gut dysbiosis and intestinal barrier failure acting as drivers of neuroinflammation along the GBA. The introduction of nonconventional biodegradable plastics,

like poly-lactic acid (PLA) plastic, might help mitigate these effects. Nevertheless, at present, non-conventional biodegradable plastics are environmentally friendly, but the toxicological implications of biodegradable microplastics on human health have been poorly investigated. Preliminary studies in the field [147,148] raise concerns about the biological impact of PLA-based bioplastics and their use as a safe alternative to petroleum-based plastics, cautioning that biodegradable alternatives are not inherently exempt from GBA-mediated neurotoxicity.

4. Plastamination in the Brain: A Focus on PD

4.1. Neuroinflammation and PD: α-Syn Deposition and Spreading

PD is a progressive neurodegenerative disorder primarily characterized by the selective degeneration of dopaminergic neurons (DAn) in the SNpc, whose axons project to the dorsal striatum, the principal input nucleus of the basal ganglia involved in motor control, goal-directed behavior, and motor learning [29,149–151]. The resulting depletion of striatal dopamine disrupts the activity of cortico-basal ganglia–thalamocortical circuits, ultimately leading to the cardinal motor manifestations of PD, including resting tremor, bradykinesia, and muscular rigidity [152].

A defining neuropathological feature of PD is the progressive accumulation of intracellular protein aggregates, which initially appear in the lower brainstem and olfactory structures before extending to limbic regions and, in later stages, to the neocortex [153,154]. These inclusions, termed Lewy bodies (LBs) within neuronal cell bodies and Lewy neurites (LNs) within neuronal processes, are primarily composed of insoluble fibrillar aggregates of misfolded α-syn [29,155].

According to the Braak staging hypothesis, PD pathology may originate in α-syn-expressing neurons outside the nigrostriatal dopaminergic system, including neurons of the olfactory pathways and the enteric nervous system [156]. Misfolded α-syn released into the extracellular space may subsequently be internalized by anatomically connected neurons, thereby promoting the progressive propagation of pathological α-syn throughout the nervous system [154,157]. Although the precise mechanisms underlying this process remain under investigation, accumulating evidence indicates that glial cells, particularly microglia and astrocytes, actively participate in α-syn transmission [158]. Owing to their phagocytic properties, these cells efficiently internalize α-syn preformed fibrils (PFFs) and can subsequently release α-syn-containing extracellular vesicles (EVs), which are readily taken up by neighboring neurons. Because neurons appear to be less efficient than glial cells in eliminating internalized α-syn species, intracellular accumulation is favored, ultimately promoting the formation of Lewy pathology [158].

Among the different conformational states of α-syn, soluble oligomers and protofibrils are considered the most neurotoxic species. Their preferential accumulation at presynaptic terminals disrupts synaptic transmission, impairs neurotransmitter release [159], and compromises synaptic plasticity within basal ganglia circuits [160]. As the disease progresses, pathological α-syn is thought to propagate retrogradely from dopaminergic axon terminals toward neuronal somata, contributing to progressive neuronal dysfunction and degeneration across multiple brain regions, with the greatest vulnerability observed in SNpc dopaminergic neurons [161,162].

Although degeneration of nigral dopaminergic neurons represents the hallmark pathological feature responsible for the motor symptoms of PD, growing evidence indicates that synaptic dysfunction and α-syn pathology develop long before substantial neuronal loss becomes clinically evident. Lewy pathology and synaptic alterations have been detected in cortical regions, including the prefrontal and cingulate cortices, during the prodromal phase of the disease and are believed to contribute to the development of non-motor

manifestations such as sleep disturbances, mood disorders, cognitive impairment, and gastrointestinal dysfunction [163]. Importantly, these prodromal symptoms are increasingly recognized as predictors of an elevated risk of developing PD [164].

Collectively, these findings underscore the importance of elucidating the molecular mechanisms governing α-syn aggregation, release, intercellular transmission, and clearance. A better understanding of these processes may facilitate the identification of novel disease-modifying strategies capable of interfering with PD pathogenesis during its earliest, preclinical stages.

4.2. α-Syn and Neuroinflammation in PD

Chronic neuroinflammation is increasingly recognized as a major contributor to the pathogenesis and progression of several neurodegenerative disorders, including PD [165,166]. This persistent inflammatory state is characterized by sustained activation of microglia and astrocytes, together with increased production of pro-inflammatory cytokines and ROS. Consistent with this view, elevated concentrations of TNF-α, IL-1β, IL-6, TGF-β, and IFN-γ have been detected in both the brain and peripheral circulation of patients with PD [167,168].

Among the molecular factors driving neuroinflammation, α-syn has emerged as a central mediator. Increasing evidence indicates that extracellular α-syn aggregates, particularly oligomeric and fibrillar species, activate microglia, thereby amplifying innate immune responses within the CNS [169]. As the resident immune cells of the brain, microglia continuously survey the neural environment and regulate multiple pathways involved in neuronal survival and cell death. Upon exposure to pathological α-syn, microglia undergo a profound phenotypic transition toward a pro-inflammatory state characterized by amoeboid morphology, enhanced proliferation, increased production of nitric oxide and intracellular ROS, and elevated secretion of inflammatory cytokines [170,171]. These responses are largely mediated by the interaction of α-syn with Toll-like receptor 2 (TLR2), which activates downstream inflammatory signaling pathways.

Experimental evidence further supports the close relationship between α-syn pathology and microglial activation. Ex vivo brain slices obtained from rats overexpressing the human α-syn gene (SNCA) exhibit α-syn aggregate deposition, robust microglial activation, and altered production of pro-resolving lipid mediators [172]. These changes are accompanied by selective degeneration of dopaminergic neurons within the substantia nigra, whereas neighboring dopaminergic neurons in the ventral tegmental area remain relatively spared, highlighting the selective vulnerability of the nigrostriatal pathway [173].

Sustained microglial activation also compromises autophagic and lysosomal function, thereby reducing the clearance of damaged organelles and misfolded proteins, including α-syn aggregates [174]. Consequently, α-syn not only initiates chronic neuroinflammatory responses but also impairs the cellular mechanisms responsible for its own degradation, establishing a self-perpetuating pathogenic loop that further accelerates neuronal dysfunction and disease progression [175]. In addition, prolonged microglial activation has been associated with necroptosis, a regulated inflammatory form of cell death triggered by receptor-interacting kinases downstream of TNF-α signaling. Increasing evidence suggests that this pathway may also contribute to PD pathogenesis [176,177].

Astrocytes, the most abundant glial cell population in the CNS, also play a critical role in PD-associated neuroinflammation. Under physiological conditions, astrocytes support neuronal metabolism, regulate synaptic transmission, and maintain blood-brain barrier integrity. During disease progression, however, reactive astrocytes acquire a pro-inflammatory phenotype that contributes to dopaminergic neurons degeneration through the release of cytokines, glutamate, and other neurotoxic mediators. Pathological α-syn can

be directly internalized by astrocytes through endocytic mechanisms, triggering intracellular inflammatory signaling, calcium dysregulation, mitochondrial complex I dysfunction, excessive ROS generation, lipid peroxidation, and ultimately apoptotic cell death [176,178].

A close interplay between α-syn pathology and inflammation has also been demonstrated in experimental models. Overexpression of human α-syn markedly enhances the neurodegenerative effects of systemic inflammatory stimulation induced by lipopolysaccharide administration, resulting in substantial dopaminergic degeneration in the substantia nigra that is not observed following either insult alone [179]. These findings support the concept that environmental inflammatory stimuli may synergize with an individual's genetic susceptibility to α-syn misfolding and aggregation, thereby promoting synaptic dysfunction, progressive degeneration of the nigrostriatal dopaminergic system, and ultimately the development of Parkinson's disease.

4.3. MPs and NPs as Emerging Environmental Contributors to Parkinson's Disease

The presence of MNPs in human tissues has prompted growing interest in their possible contribution to multisystem disorders. Their widespread persistence in terrestrial and aquatic ecosystems, together with their increasing accumulation in the food chain, has raised significant concerns regarding their long-term effects on human health. Clinical observations have suggested associations between confirmed MNP exposure and recurrent symptoms involving the gastrointestinal, cardiovascular, endocrine, and nervous systems, although the available evidence remains limited and does not yet establish causality.

Of particular concern is the detection of MNPs within the CNS, where their presence has been associated with pathological processes implicated in several neurological disorders, including PD. Owing to their nanoscale dimensions, NPs appear particularly relevant for neurological health because they readily interact with biological membranes, cross the BBB, and accumulate within the CNS [38]. In addition to hematogenous transport, these particles may reach the brain through the olfactory pathway and the gut-brain axis, further increasing their potential for neural exposure. Among the environmental risk factors most consistently associated with PD are pesticides, herbicides, heavy metals, and industrial solvents [180–182]. Many of these toxicants preferentially affect dopaminergic neurons by disrupting their physiological function and reducing striatal dopamine release, ultimately reproducing key pathological and behavioral features of PD in experimental models [183].

These environmental factors are indeed strongly involved in PD development; however, it is believed that they mostly act in concert with genetic susceptibility. For instance, mutations of the LRRK2 gene are responsible for most of the known heritable forms of PD [184], and higher sensitivity to environmental toxins has been reported in a mouse model of the LRRK2 gene mutation [185]. Similarly, GBA gene mutations have been recognized as risk predictors of PD [186] through an underlying mechanism of upregulated inflammatory responses to stressing agents [187]. Analogous results were obtained in studies on a genetic model of PD with α-syn overexpression [179]. The overall picture arising from these experimental data on PD etiology points to neuroinflammatory processes triggered by environmental toxic agents, ultimately causing α-syn misfolding and aggregation, whose harmfulness is inscribed within a range of possibilities linked to individual genetic predisposition and vulnerability.

More recently, MPs and nanoplastics (NPs) have also emerged as potential environmental contributors to PD pathogenesis [188].

Experimental studies have shown that neuronal exposure to MNPs induces oxidative stress, mitochondrial dysfunction, impairment of autophagic pathways, and ultimately apoptotic cell death [189]. These alterations closely resemble several cellular mechanisms

implicated in PD and provide a biological rationale for investigating a possible relationship between plastic exposure and neurodegeneration.

It should also be added that, similarly to other toxic environmental factors, NPs have been shown to act synergistically with genetic predisposition to promote anomalous protein aggregation in an AD animal model [190]. This observation reinforces the hypothesis that environmental NPs may favor the anomalous aggregation of α-syn fibrils and that the final outcome in terms of PD development might be dependent on additional predisposing factors linked to the individual genetic profile.

In this regard, recent studies have suggested that both MPs and NPs may directly influence α-syn biology. In particular, PE-MPs, PVC-MPs, and PS-MPs have been reported to alter the secondary structure of α-syn by decreasing the content of α-helices and increasing the contents of β-turns, β-sheets, and random coils. Notably, PS-MPs exhibit the greatest propensity to promote the formation of amyloidogenic oligomers, an effect that has been attributed to their small particle size (100 nm) [191]. Another study on the binding behavior of human α-syn following interaction with PE-NPs indicated the transition of α-syn from an open helical to a compact conformation, enhancing intramolecular interactions [192]. NPs exhibit a high affinity for wild-type α-syn, facilitating its misfolding and accelerating the formation of amyloid aggregates [35]. These aggregated species display enhanced neurotoxicity and can trigger inflammatory activation of microglia [193]. Moreover, experimental evidence indicates that both NPs and α-syn fibrils are internalized through clathrin-mediated endocytosis and subsequently accumulate within lysosomes, where mild lysosomal dysfunction delays α-syn degradation and promotes its intracellular persistence [38].

Interestingly, intracerebral administration of NPs alone results in limited diffusion within the brain parenchyma, whereas co-administration of NPs with α-syn fibrils promotes the dissemination of both pathological α-syn and NPs across interconnected brain regions [38]. These observations suggest that interactions between NPs and α-syn may facilitate the propagation of pathological protein aggregates through neuronal networks. Furthermore, intrastriatal administration of NPs alone has been reported to induce *de novo* α-syn aggregation within dopaminergic neurons of wild-type mice, although this effect was observed only in a subset of experimental animals [38].

While these findings support the hypothesis that NPs may accelerate pathological processes associated with PD, they should be interpreted cautiously until replicated in independent experimental settings.

Indeed, despite these promising experimental observations, important limitations remain. For example, most available studies have employed animal models or cultured cells exposed to relatively high concentrations of MPs or NPs that may not accurately reflect chronic human environmental exposure.

Thus, although experimental evidence increasingly indicates that exposure to MNPs may exert neurotoxic effects, convincing epidemiological data demonstrating an association between MNP exposure and neurological disorders in humans remain scarce. This is linked to methodological limitations, including small study populations, predominantly cross-sectional designs, and inconsistent approaches to exposure assessment, all of which limit the ability to establish causal relationships. Future research should prioritize the development of standardized methods for MNP detection, detailed analyses of region-specific brain distribution, and well-designed longitudinal studies combining exposure biomarkers with clinical, neuroimaging, and neuropathological outcomes.

In addition, the detection and quantification of plastic particles in human tissues, particularly in lipid-rich organs such as the brain, remain technically challenging. Sample contamination, tissue processing, and analytical sensitivity may all contribute to false-

positive or inconsistent results [137,194]. The integration of complementary analytical techniques and standardized detection protocols will therefore be essential to improve the reliability and reproducibility of future studies [195].

Overall, current evidence supports the hypothesis that micro- and nanoplastics may contribute to molecular pathways involved in PD pathogenesis, including oxidative stress, neuroinflammation, impaired proteostasis, and α-syn aggregation. However, whether environmental exposure to these particles represents an independent risk factor for PD in humans remains to be established. Future studies should focus on long-term, low-dose exposure paradigms that better reproduce real-life conditions and clarify the contribution of environmentally relevant plastic mixtures generated by both environmental weathering and biological degradation. These advances will be crucial for determining the validity and clinical relevance of the emerging concept of "plastic brain."

5. Conclusions

MNPs have emerged as widespread environmental contaminants with the potential to adversely affect multiple physiological systems, including the CNS. Experimental evidence indicates that these particles can cross biological barriers, accumulate in neural tissues, and disrupt cellular homeostasis through oxidative stress, mitochondrial dysfunction, impaired proteostasis, and sustained neuroinflammatory responses. Together, these alterations create a cellular environment that favors neuronal dysfunction and may contribute to the molecular pathways implicated in neurodegenerative disorders, including PD.

Current findings also suggest that MNPs may influence PD pathogenesis by promoting α-syn misfolding and aggregation, impairing intracellular protein clearance, and amplifying glia-mediated inflammatory responses. Beyond their direct neurotoxic effects, MNPs may interfere with systemic processes, including GBA communication and neuroendocrine regulation, highlighting the complex and multifactorial nature of their biological impact.

Overall, while experimental evidence and the first detection of MNPs in the blood of PD patients and within post-mortem brains [137,138] support the potential health risks of MNPs, there is a need for further studies in the field to clarify their long-term impact under realistic exposure conditions and to better assess their relevance for human health. Despite these advances, the available data remains largely derived from in vitro studies and experimental animal models employing exposure paradigms that often exceed environmentally relevant conditions. In fact, environmental plastamination comprises different mixtures of plastics, with unique compositions of plastic debris exhibiting different sizes, forms and shapes. In addition, commercially available plastics mostly consist of spherical particles of specific sizes and types, often used at concentrations that do not parallel those detected in biological fluids.

Furthermore, epidemiological and clinical data demonstrating an association between MNP exposure and neurological disorders in humans remain scarce, are derived from small cohorts, and have largely been published in the last 24 months. Moreover, methodological challenges associated with sampling, detection and quantification of MNPs in human tissues are not standardized, thus limiting the interpretation of epidemiological and clinical findings. Consequently, a causal relationship between chronic environmental exposure to MNPs and the development of neurological diseases such as PD in humans has not yet been established. To fill the large knowledge gap in the field and to better define the contribution of MNPs to neurodegenerative disease, future research should therefore prioritize standardized analytical methodologies, environmentally relevant long-term exposure models, and well-designed longitudinal human studies combining clinical, neuroimaging, and neuropathological outcomes to the exposome. In this context, occupational exposure risk to MPs is also becoming a growing area of concern [196]. A cross-sectional study

conducted on plastic factory staff to examine exposure levels to MPs before and after work shifts revealed the presence of plastic fibers with a size ≥1000 μm on hands, hair, facial skin, and saliva, with hair and saliva samples having the highest and lowest number of MPs, respectively [197]. Hence, the importance of providing adequate protection to reduce exposure and thorough monitoring to assess risks for occupationally exposed populations such as factory workers or waste handlers, thus protecting public health.

Particular attention should also be devoted to understanding the combined effects of different plastic particles, associated chemical additives, and co-contaminants to limit Trojan horse effects, as well as the biological consequences of environmentally weathered plastics.

Once considered an environmental trouble mainly restricted to aquatic environments, plastamination today is an environmental, economic, and social problem with impacts on health [1]. Nowadays, removing plastic from everyday life is quite unrealistic, but exposure to MNPs is inevitable since they are present in air, soil, freshwater and saltwater and enter the food chain. The aforementioned critical issues, in particular methodological inconsistencies and the paucity of epidemiological and clinical studies in the field, prevent the establishment of definitive size-based thresholds for regulatory purposes and mechanistic studies. The Estimated Daily Intake itself is quite indicative [198], and currently, it is not possible to ascertain any tolerable daily intake. Hence, there is a large knowledge gap regarding what the average consumer is ingesting and what future regulatory agencies may need to consider for routine monitoring and limitations for daily human intake from various food, beverage, and consumer by-products.

New strategies have emerged for integrating plastics into a circular economy, and the European Union (EU) has adopted several actions to make all plastic packaging reusable or recyclable by 2030. In this respect, non-conventional biodegradable plastics such as PLA plastic have been introduced in the market as eco-friendly alternatives to conventional plastics. Although bio-plastics can mitigate the impact of environmental plastamination, their possible toxicity on human health has been poorly investigated. Preliminary studies in the field [147,148] raise concerns about the biological impact of bio-plastics, warning that biodegradable alternatives are not inherently exempt from harming cell functions or GBA-mediated neurotoxicity. Hence, there is a need for further studies to fill the knowledge gap regarding the actual health safety of biodegradable plastics.

In vitro and in vivo antioxidants like N-acetylcysteine or glutathione reduce MNP toxicity by counteracting oxidative stress damage [51–53]. Hence, healthy lifestyle and dietary patterns that support antioxidant defenses, inflammatory balance, and gut health may be useful to preserve brain functions and promote successful aging; nevertheless, we are far from considering dietary intervention and the supplementation of antioxidant scavengers as effective strategies to counteract "plastamination" in the human body.

Hence, a multidisciplinary One Health approach combining biological, medical, engineering, managerial and cultural perspectives may be useful to offer a systematic and multidimensional reading of the phenomenon, promote conscious and sustainable use of plastics in society, improve waste management, guide future environmental policies and develop effective strategies aimed at reducing plastic-related risks to human brain health.

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