# Placeholder ’cause old one was too cringey

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# Abstract

*Keywords*: microplastics, immunity, neuroinflammation

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# Introduction

The ubiquitous presence of microplastics (MPs) and nanoplastics (NPs) is a defining global environmental crisis of the 21st century. First named by ([Thompson et al., 2004](#ref-thompsonLostSeaWhere2004)), microplastics are defined as particles with diameters from to , while nanoplastics have diameters smaller than . Given their non-degradable nature and ability to carry adsorbed toxicants, MNPs represent a significant form of environmental pollution whose full impact is only beginning to be understood.

The mechanism driving this systemic harm is centered around the Gut-Brain-Axis (GBA). This axis represents the bidirectional communication pathway linking the nervous system and the immune system, thereby coordinating the body’s response to both internal and external stressors. It is also through this pathway that environmental insults can translate into central nervous system (CNS) dysfunction. This paper argues that MNPs exposure poses an alarming neurological risk by facilitating the particles’ access to the brain, either directly or indirectly. Once in the CNS, these particles can trigger a sustained, non-resolving state of neuroinflammation via persistent microglial activation—ultimately resulting in cognitive and behavioral deficits.

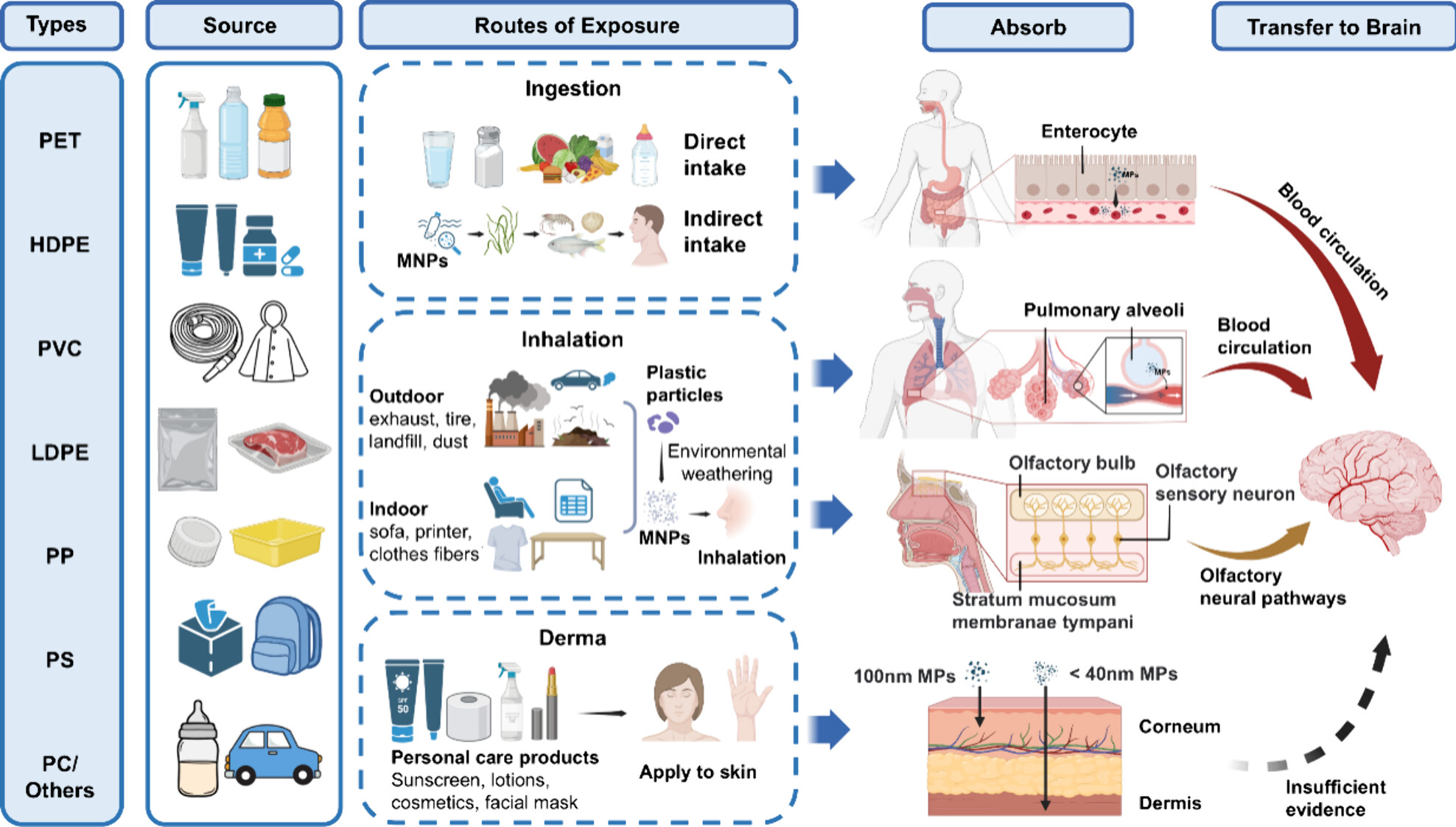
# MP Transport and Crossing the Blood-Brain Barrier (BBB)

## Routes of Entry

MNPs enter the body via several primary routes. The most prevalent pathways are ingestion—mainly from contaminated food and drinking water—and inhalation—often from airborne particles such as indoor dust and synthetic clothing fibers. While dermal absorption remains a possibility, it is generally considered a less significant route. [Figure 1](#fig-entry-routes) the translocation pathway of MNP to the brain. Recent research discovered that nanoplastics appear to be the most dangerous type, as their diminutive size facilitates rapid entrance into the bloodstream and distribution throughout the body ([Kopatz et al., 2023](#ref-kopatzMicroNanoplasticsBreach2023)).

Figure 1

Environmental Sources and MNPs’ Pathways to the Brain



*Note*. This diagram showcases the types of plastics, where they come from, and how they enter the body. The American Plastics Industry Association created the SPI code (SPI-Code) to provide a standard method for classifying plastics. Nanoplastics are best at traversing through the BBB into the brain due to their diminutive size. Reprinted from Ma, Q., Lei, J., Pang, Y., Shen, Y., & Zhang, T. (2025). Neurotoxicity of Micro- and Nanoplastics: A Comprehensive Review of Central Nervous System Impacts. Environment & Health. https://doi.org/10.1021/envhealth.5c00087.

## Blood-Brain Barrier Structure

The CNS has a sophisticated shield called the Blood-Brain Barrier (BBB) that separates brain matter from the rest of the body. This structure is formed by specialized cerebral endothelial cells connected by tight junctions, along with pericytes and astrocytes ([McConnell & Mishra, 2022](#ref-mcconnellCellsBloodbrainBarrier2022)). The BBB effectively limits the passage of foreign substances, pathogens, and large molecules from the circulatory system into the brain, which helps maintain the neural microenvironment’s homeostasis.

## Translocation Hypotheses

There are many hypotheses regarding the MNPs’ route through the BBB. One such route is paracellular diffusion, which in theory could allow even smallest nanoplastic particles to pass, although this pathway is heavily restricted ([Campbell et al., 2012](#X004f712ec1095099a0c1c2348f1de96e549812f); [Winiarska et al., 2024](#ref-winiarskaPotentialImpactNano2024)). A more probable mechanism is endocytosis—where NPs are internalized by the brain endothelial cells and subsequently exocytosed into the brain interstitial fluid ([Hamed et al., 2022](#ref-hamedNeurotoxicEffectsDifferent2022)). A third, highly discussed hypothesis is the “Trojan Horse effect”. This scenario presumes that MNPs are first phagocytized by circulating immune cells, which then act as vectors to carry them across the BBB ([Li et al., 2025](#ref-liNewEvidenceMechanisms2025)).

## Associated Toxicants

A critical factor that exacerbates MNP-related neurotoxicity is associated toxicants. MNPs, due to their high surface-to-volume ratio, readily absorb chemical additives and environmental pollutants, (e.g., benzo[a]pyrene, okadaic acid) ([Yan et al., 2023](#Xe629b25df5763d94ad90b0417c5c121df366051)). These chemicals also have the capability to disrupt the BBB and impair tight junction integrity, thereby allowing the plastic particles easier access to the brain tissue and synergizing the overall neurotoxic effect. ([Cheng et al., 2023](#ref-chengEffectsAdsorbedBenzoapyrene2023))

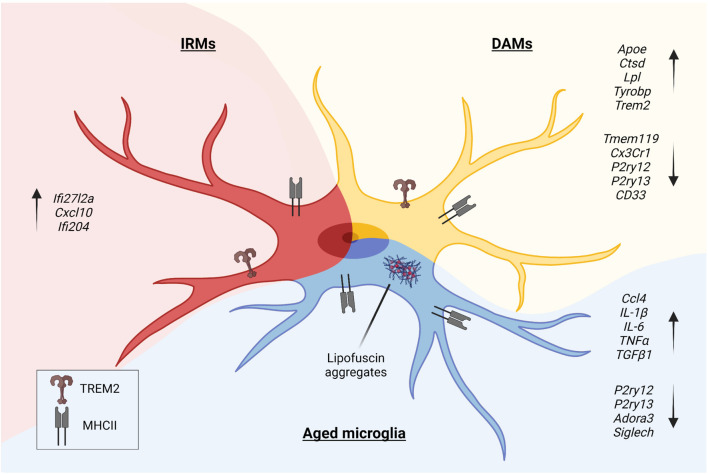
# Microglial Activation and Neuroinflammation

## The Role of Microglia

Microglial cells are the brain’s resident macrophages and the primary immune cells of the CNS. In their resting state, microglia adopt a branched morphology, actively surveying the microenvironment for pathogens, damaged cells, or misfolded proteins ([Wake et al., 2011](#ref-wakeFunctionsMicrogliaCentral2011)). When activated, these cells will rapidly undergo functional and morphological transformation, proliferate, migrate to the injury site, and engage in immunological activies—i.e., phagocytosis, antigen presentation, and the release of signaling molecules ([Yang et al., 2010](#ref-yangRoleMicrogliaCentral2010)). [Figure 2](#fig-microglia-states) showcases different transformations of microglial cells. The neuroinflammation is marked by chronic, uncontrolled activation of cells like microglia, which leads to persistent neurotoxicity and neuronal damage ([Muzio et al., 2021](#X8c4db74612eb4359854825ace8f5a75bc5d1444)).

Figure 2

Different Activation States of Microglia



*Note*. Microglia experience morphologic and phenotypic/functional changes upon activation. Shown in this drawing are Disease-Associated Microglia (DAMs), Injury-Responsive Microglia (IRMs), and aged microglia, each representing a distinct activation state. Reprinted from Muzio, L., Viotti, A., & Martino, G. (2021). Microglia in Neuroinflammation and Neurodegeneration: From Understanding to Therapy. Frontiers in Neuroscience, 15, 742065. https://doi.org/10.3389/fnins.2021.742065.

## Direct Activation Mechanism

One primary hypothesized mechanism involves the direct interaction of MNPs with microglia. As discussed in the previous section, NPs are believed capable of crossing the BBB and being taken up via phagocytosis. Being non-degradable, these particles persist within the microglial lysosome, which leads to a phenomenon coined “frustrated phagocytosis” ([Ishida et al., 2019](#ref-ishidaLivecellImagingMacrophage2019)). The inability to clear the foreign material results in chronic lysosomal stress and damage—akin to choking themselves to death ([Mularski et al., 2018](#Xc075ecd0603de099cd0d3801a41cc8bb5d7a187)). Persistent internal stress like this drives a sustained microglial activation state that remains even in the absence of a live pathogen.

## Inflammasome Pathway

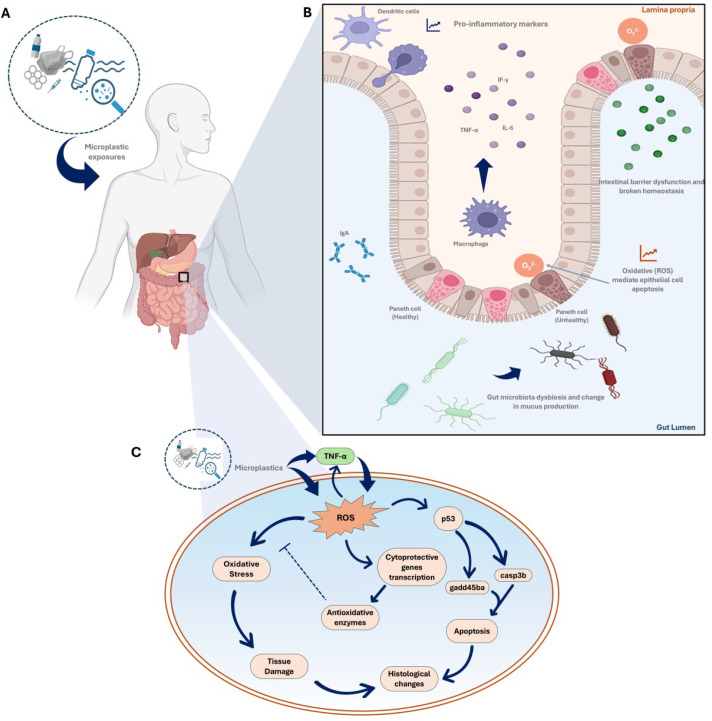
As a direct consequence of frustrated phagocytosis, an important inflammatory cascade is triggered: the NLRP3 Inflammasome. This complex is an intracellular receptor that senses danger signals, such as lysosomal rupture and the formation of reactive oxygen species (ROS), both of which are common outcomes of MP/NP internalisation by body cells. Activation of the NLRP3 inflammasome leads to the cleavage of pro-caspase-1 into active caspase-1. This activated enzyme, in turn, causes the maturation and release of pro-inflammatory cytokines, namely, Interleukin-1 (IL-1) and Interleukin-18 (IL-18) ([Harrison, 2013](#ref-harrisonChiasmaRochePartner2013); [Matousek et al., 2012](#X592a8f7e9822be7b2d667d2b74ce1e90f1cedb8)). These cytokines further propagate the inflammatory signal, recruiting additional immune cells and intensifying the neuroinflammatory cycle—contributing directly to neuronal injury ([Delantoni et al., 2023](#X7e07edb5dcf956124458476de0bb8c859e947f0)).

## Indirect Disruption via Gut-Brain Axis

Microglial activation does not require direct entry of plastic particles into the brain. Exposure in peripheral sites, particularly the gut (via ingestion) and the lungs (via inhalation), can be sufficient to drive a state of systemic inflammation. As MNPs invade and damage the intestinal and pulmonary barriers, gut bacteria and associated toxins will translocate into the bloodstream. This systemic inflammatory state results in the establishment of the GBA ([Kalyan et al., 2022](#X8aac5304898f8d6b298a94f1cf67b376bb3965d)). As such, inflammatory signals (such as pro-inflammatory cytokines), even without crossing the BBB themselves, can signal through endothelial cells and other immune cells, or directly diffuse across the BBB, practically acting as “danger messages” that trigger an indirect, secondary activation of the quiescent microglial population and extend the peripheral damage into the CNS ([Bora et al., 2024](#ref-boraMicroplasticsHumanHealth2024); [Hoogland et al., 2015](#X542999c159c4319fc9bb0895037e02ed832cecc)). [Figure 3](#fig-gut-brain-axis) demonstrates this complicated cascade, alongside the GBA.

Figure 3

Interactions Between MNPs and Human Gut



*Note*. Figure (A) shows the entry of MNPs into the body. Figure (B) is the inflammatory response caused by the invasion of MNPs—marked by the release of pro-inflammatory cytokines such as TNF- and IL-6. Figure (C) outlines the pathways of oxidative stress activated by MNP-induced inflammation. Reprinted from Bora, S. S., Gogoi, R., Sharma, M. R., Anshu, Borah, M. P., Deka, P., Bora, J., Naorem, R. S., Das, J., & Teli, A. B. (2024). Microplastics and human health: Unveiling the gut microbiome disruption and chronic disease risks. Frontiers in Cellular and Infection Microbiology, 14, 1492759. https://doi.org/10.3389/fcimb.2024.1492759.

# Consequences and Future Directions

## Observed Functional Consequences

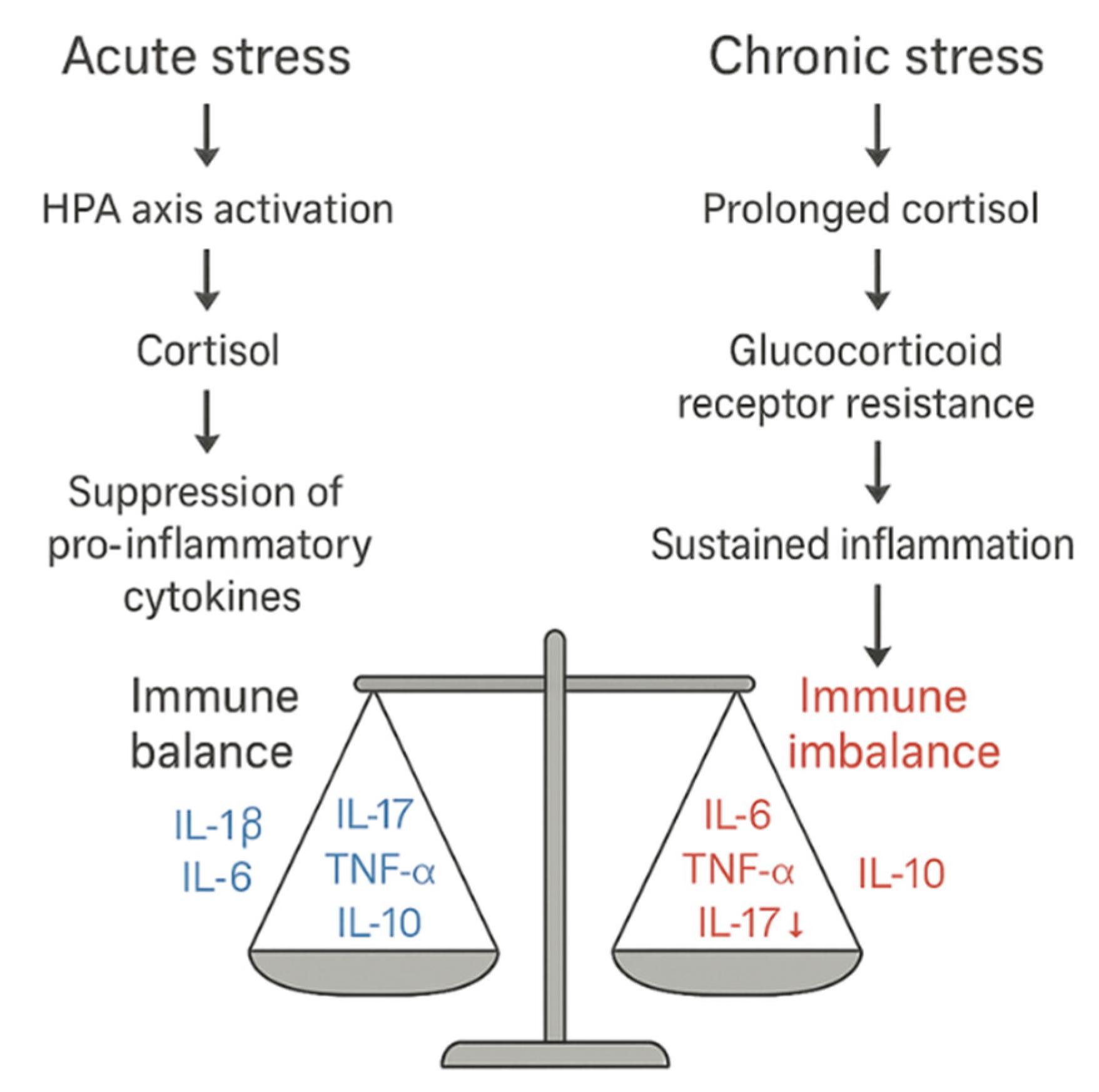
Chronic microglial activation, sustained by MNP presence or systemic inflammatory signaling, disrupts the delicate balance required for optimal neural network function. Functionally, this has been observed in animal models to cause behavior changes—such as heightened levels of anxiety and depression-like behaviors ([Chen et al., 2025](#X4b16bc5668ca674ac33f236bc5ef2112c6eea65); [Fang et al., 2023](#ref-fangRolesMicrogliaAdult2023)). This also directly impairs synaptic plasticity and neurogenesis, leading to noticable performance deficits, particularly in tasks related to learning and memory ([Bollinger & Wohleb, 2019](#ref-bollingerFormativeRoleMicroglia2019); [Cornell et al., 2021](#X187f1e143afc0a653bb3def6eeabaeeb7780a04)). These alarming outcomes suggest that MNPs contamination poses a risk to neurological health that extends beyond localized damage and impacts complex CNS functions.

## HPA Axis and Stress Hormones

Another significant systemic consequence of chronic inflammation is the disruption of the hypothalamic-pituitary-adrenal (HPA) axis, often termed the Stress Axis. Pro-inflammatory cytokines released during MNP exposure, such as TNF- and IL-6, are known stimulators of the HPA axis—which lead to increased production and release of glucocorticoids, namely, cortisol ([Jeon & Kim, 2016](#X6792e15aa4e08317f786519cd1410dba88296ce)). While an initial cortial surge is protective, exposure to inflammation signals over a long time period results in HPA dysregulation—which manifests as either hyper-activation or, paradoxically, a state of hyporesponsiveness.This impaired feedback mechanism compromises the body’s ability to manage stress and inflammation effectively, becoming a debilitating cycle where chronic inflammation leads to HPA axis exhaustion, which in turn further impairs the immune system’s ability to self-regulate [Bertollo et al. ([2025](#Xc95cded9e6e58855cd5d1d479b0aa4c70690718)); ([Nunez et al., 2025](#ref-nunezChronicStressAutoimmunity2025)). This cycle can be seen in [Figure 4](#fig-acute-chronic-HPA).

Figure 4

MNP-driven HPA Axis Dysregulation Cycle



*Note*. The shift from a protective acute stress response (Left) to chronic endocrine and immune dysregulation (Right), a process exacerbated by sustained inflammatory signals from MNP exposure. During acute stress, the HPA axis releases Cortisol which maintains immune homeostasis by restraining pro-inflammatory cytokines (IL-1, IL-6, TNF-, IL-17) However, chronic MNP-induced inflammation leads to persistent HPA activation, resulting in Glucocorticoid Receptor (GR) resistance. This impaired feedback loop prevents effective immune suppression, thereby sustaining high levels of pro-inflammatory cytokines, driving chronic inflammation—and potentially autoimmunity. Reprinted from Nunez, S. G., Rabelo, S. P., Subotic, N., Caruso, J. W., & Knezevic, N. N. (2025). Chronic Stress and Autoimmunity: The Role of HPA Axis and Cortisol Dysregulation. International Journal of Molecular Sciences, 26(20), 9994. https://doi.org/10.3390/ijms26209994.

## Treatment and Prevention Angle

Micro- and nanoplastic (MNP) exposure is a modern, global issue that requires an urgent, dual strategy: prevention alongside treatment. Prevention is paramount, focusing on policy changes to maximally reduce plastic production and subsequent environmental dispersal. Simultaneously, new technologies must be developed for environmentally-friendly alternatives and plastic remediation. From a biomedical standpoint, targeted treatment strategies could involve developing specific anti-inflammatory agents that target known microglial activation pathways, such as selective inhibitors of the NLRP3 Inflammasome. From a biomedical standpoint, targeted treatment strategies could involve developing specific anti-inflammatory agents that target known microglial activation pathways, such as selective inhibitors of the NLRP3 Inflammasome. Such interventions could potentially decouple inflammatory signaling from the physical presence of non-degradable particles.

## Conclusion & Future Research

The evidence and analysis presented here demonstrates that MNPs are more than environmental contaminants—they are also significant neurotoxic agents, capable of long-term harm to both humans and animals alike. Their ubiquitous presence, combined with the alarming capability of nanoplastics to traverse biological barriers establishes a grave threat to CNS health. A sustained neuroinflammatory state caused by frustrated phagocytosis, NLRP3 inflammasome activation, and HPA axis dysregulation manifests as behavioral deficits and cognitive impairment. This proves that MNP exposure extends far beyond localized cellular damage.

Moving forward, a multi-disciplinary approach is crucial to translate these mechanistic findings into actionable public health strategies. Future research should work on large-scale human epidemiological studies to correlate MNP body burden with specific neurological and cognitive outcomes. There is also an urgent need for targeted therapeutic development focused on decoupling inflammatory signaling from the presence of non-degradable particles; BBB-permeable NLRP3 Inflammasome inhibitors should be a good starting point. Further mechanistic work must precisely characterize the inflammatory signals that transmit neurotoxicity from the peripheral gut to the CNS, in order to identify specific signaling molecules that trigger secondary microglial activation. Finally, to accurately reflect real-world exposure, future investigations must move beyond pristine polystyrene and prioritize the toxicity assessment of environmentally-aged and chemically-altered MNPs. While targeted biomedical interventions offer hope, the most effective long-term solution is proactive, globally-coordinated prevention to dramatically reduce plastic production and environmental dissemination.

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