brain sciences

MDPI

Review

Nanoplastics and Neurodegeneration in ALS

Andrew Eisen [1,*], Erik P. Pioro [1], Stephen A. Goutman [2] and Matthew C. Kiernan [3]

[1] Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, BC V6S 1Z3, Canada; erik.pioro@ubc.ca
[2] Department of Neurology, University of Michigan, Ann Arbor, MI 48109, USA; sgoutman@med.umich.edu
[3] Neuroscience Research Australia, Randwick, Sydney, NSW 2031, Australia; matthew.kiernan@neura.edu.au
* Correspondence: eisen@mail.ubc.ca

Abstract: Plastic production, which exceeds one million tons per year, is of global concern. The constituent low-density polymers enable spread over large distances and micro/nano particles (MNPLs) induce organ toxicity via digestion, inhalation, and skin contact. Particles have been documented in all human tissues including breast milk. MNPLs, especially weathered particles, can breach the blood–brain barrier, inducing neurotoxicity. This has been documented in non-human species, and in human-induced pluripotent stem cell lines. Within the brain, MNPLs initiate an inflammatory response with pro-inflammatory cytokine production, oxidative stress with generation of reactive oxygen species, and mitochondrial dysfunction. Glutamate and GABA neurotransmitter dysfunction also ensues with alteration of excitatory/inhibitory balance in favor of reduced inhibition and resultant neuro-excitation. Inflammation and cortical hyperexcitability are key abnormalities involved in the pathogenic cascade of amyotrophic lateral sclerosis (ALS) and are intricately related to the mislocalization and aggregation of TDP-43, a hallmark of ALS. Water and many foods contain MNPLs and in humans, ingestion is the main form of exposure. Digestion of plastics within the gut can alter their properties, rendering them more toxic, and they cause gut microbiome dysbiosis and a dysfunctional gut–brain axis. This is recognized as a trigger and/or aggravating factor for ALS. ALS is associated with a long (years or decades) preclinical period and neonates and infants are exposed to MNPLs through breast milk, milk substitutes, and toys. This endangers a time of intense neurogenesis and establishment of neuronal circuitry, setting the stage for development of neurodegeneration in later life. MNPL neurotoxicity should be considered as a yet unrecognized risk factor for ALS and related diseases.

Keywords: ALS; micro/nanoplastics; exposome; gut–brain axis; TDP-43

Citation: Eisen, A.; Pioro, E.P.; Goutman, S.A.; Kiernan, M.C. Nanoplastics and Neurodegeneration in ALS. *Brain Sci.* **2024**, *14*, 471. https://doi.org/10.3390/brainsci14050471

Academic Editor: Roberto Cilia

Received: 18 April 2024
Revised: 2 May 2024
Accepted: 6 May 2024
Published: 7 May 2024

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegeneration causing paralysis of skeletal and respiratory muscles and cognitive decline [1,2]. ALS mechanisms are broad [3], and the molecular subtypes underlying disease vary among patients [4]. In parallel, genetic variability in ALS is also inconstant; most ALS patients lack a disease-causing monogenic mutation, but numerous risk-genes have been identified, each having small effects [5], emphasizing the need to identify non-genetic ALS risk factors. Of increasing concern is the role the life course of environmental exposures—the exposome—plays in ALS risk [6]. This is especially important as these exposures may be modifiable and offer the hope of disease prevention for ALS [7], and other neurological diseases more broadly [8].

Exposures to toxicants or xenobiotics negatively impact health directly, by impairing chemical reactions or enzymes, impairing ion channel function, disrupting the cellular membrane, or causing oxidative stress or inflammation [9–11]. Indirect health effects may result from the metabolic products of a toxicant, as opposed to the toxicant itself. Alternatively, exposures can also promote epigenetic modifications [12,13], which alter

the output without changing the DNA itself. Epigenetic modifications include DNA methylation, histone modifications [14], and non-coding RNAs and microRNAs [15].

Mislocalization and extra-nuclear aggregation of TAR DNA-binding protein 43 (TDP-43) is a pathological hallmark of ALS. Exposure to environmental toxicants, including dioxins, polychlorinated biphenyls (commonly used in plastics), and polycyclic aromatic hydrocarbons or heavy metal neurotoxicants increases the level of TDP-43, providing a link between environmental factors and TDP-43-associated disorders [16].

Even though plastic production has increased exponentially since the 1950s [17,18], recognition of microplastics as pollutants of risk to humans is only recent [19,20], and their potential as a risk factor in the pathogenesis of neurodegeneration has received very limited attention. Given the ubiquitous availability of MNPLs in daily life, this may be an emerging ALS risk given the overlap with ALS mechanisms, and thus there is a need for further research. Human exposure to microplastics is predominantly through ingestion, which can negatively impact the gut microbiome and gut–brain axis [21,22] and alterations of gut microbiota may contribute to the etiology of ALS and its progression [23–25].

Here, we justify the concern of MNPLs in the setting of ALS exposome research, discuss sources of micro and nanoplastics and their toxicologic properties in humans, and the potential mechanistic links with ALS.

2. The Exposome

As noted by Wild [26], the "exposome encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards". Wild reflected that an increased burden of human disease may result from more prevalent environmental exposures interacting with potentially frequent but low-penetrant genetic variants [27], and advocated for improved exposure biomarkers [26]. There is an increasing appreciation of the role the exposome plays in influencing neurodegenerative diseases [8], along with a greater emphasis on research supporting the neural exposome [28]. In ALS, there are recurrent exposure types that contribute to disease risk, [6] such as pesticides, heavy metal exposure, and physical activity. A complex aspect of this exposure research is accounting for the combined effects of multiple exposures on a health outcome, such as via the use of environmental risk scores [29–31]. Certainly, ongoing research is needed to identify specific exposure that most influences risk either alone or in combination with other related or disparate exposures [32].

3. Micro- and Nanoplastics (MNPLs)

The term microplastics was coined in 2004 and used to describe small plastic particles. However, there is still no all-inclusive definition that accurately encompasses all criteria that could potentially describe what a microplastic is [33]. Microplastics are defined as "...any synthetic solid particle or polymeric matrix, with regular or irregular shape, and with size ranging from 1 µm to 5 mm, of either primary or secondary manufacturing origin, which are insoluble in water" [33]. Plastics are of many different shapes, sizes, and colors, made from polymers with multiple chemical additives [34]. Primary particles are released directly into the environment from many sources, whereas secondary (weathered) particles result from degradation and fragmentation [35,36]. Opening plastic packages can generate microplastics in daily life, regardless of the method of opening and plastic target [37]. Most plastic polymers are low-density polyethylene, polyvinyl chloride, polystyrene, polypropylene, and polyethylene terephthalate [9,38]. Non-stable plastics are subject to fragmentation through photodegradation and erosion, forming toxic micro/nano plastics [39]. Not only do plastics contain hazardous chemicals through their manufacture, including plasticizers (e.g., bisphenol-A), UV stabilizers, lubricants, dyes (e.g., heavy metals), and flame retardants, they also serve as vectors for some of these same toxic chemicals found in the environment [40,41].

Biodegradable plastics have been commercialized in the manufacturing of various types of products such as garbage bags, compost bags, poly bags and agricultural mulch

films and can decompose after disposal to the environment by biodegradation processes involving the use of enzymes produced by bacteria and microorganisms to break the plastic chemical bonds, producing CO_2 and H_2O. This leads to large numbers of plastic particles with greater surface areas for interactions with the surrounding environment [42]. However, of greatest concern are those synthesized from petroleum [43]. Common plastic polymers found in the environment include polyethylene, polypropylene, polyvinyl chloride, and polyethylene terephthalate [44]. Although plastics are highly durable, they can degrade over time, releasing microplastics (1 μm–5 mm particles) and nanoplastics (<1 μm particles) [43].

4. Sources of MNPLs

MNPLs accumulate in the environment and are detectable in air, water, and soil [43–46]. Human exposure routes are dermal, oral ingestion (contaminated water, food, or dust or release from plastic packaging), and inhalational [42,44,47]. Ingestion is responsible for the greatest exposure in humans [47]. Of concern is that the levels of MNPLs in the environment are projected to increase [48].

Small oceanic plastic fragments were first reported in the 1970s when Thor Heyerdahl, the Norwegian adventurer and ethnologist, captained an expedition across the Atlantic Ocean from Morocco to Barbados. Over the course of his journey, he encountered abundant plastic waste [49]. Microplastics are widespread in all ecosystems [34,50–52] including in many human foods and drinking water [53] and are defining a new epoch dubbed the Plasticene [54]. When airborne, they can travel long distances from their original source [55]. MNPLs can be purposely produced (primary), as a consequence of fragmentation and degradation (secondary) or released from synthetics microfibers of clothing [43]. Primary sources include industrial detergents and cosmetics [44] (see Table 1). Further, plasticizers including phthalic acid esters (PAEs) can co-pollute, thereby increasing the toxicity of these particles [44]. MNPLs in soil and water can also absorb pathogenic heavy metals [56], and organic pollutants, such as persistent organic pollutants [44,45,57].

Table 1. Sources of MNPLs.

1. Primary Sources:
Breakdown of larger plastic items such as packaging materials, bottles, and synthetic textiles.
Microbeads used in personal care products.
Emission of plastic particles during manufacturing processes.
2. Secondary Sources:
Effects due to weathering, sunlight, and wave action.
Tire wear with release of microplastic particles.
Deterioration of road markings containing microplastics.
3. Urban Runoff:
Flushing of microplastics into rivers and oceans.
Incomplete removal of microplastics during wastewater treatment.
4. Atmospheric Deposition:
Microplastics transported by the wind and deposited from the atmosphere.
5. Agricultural Runoff:
Plastic mulching with release of microplastics into the soil.
Plastic particles from irrigation systems.
6. Natural Sources:
Natural weathering can release microplastics from rocks and sediments.

5. Human Exposure

Humans are primarily exposed to MNPLs through ingestion, and estimates indicate that humans ingest tens of thousands to millions of MNPLs annually (several milligrams daily). The main plastic-containing ingestants are drinking water, seafood, honey, beer, table salt, and milk [58], and recently identified leafy vegetables. Inhalation [59,60] and dermal contact [61] occur less frequently [58,62–64], and some developed drug delivery systems also expose human beings to MNPLs via parenteral routes, including intravenous and intracranial/brain application [65]. Neonates and infants are exposed to MNPLs through breast milk and milk substitutes [66]. Plastic bottle caps, plastic teabags and infant feeding bottles can release a considerable number of MNPLs [62,67] (see Figure 1).

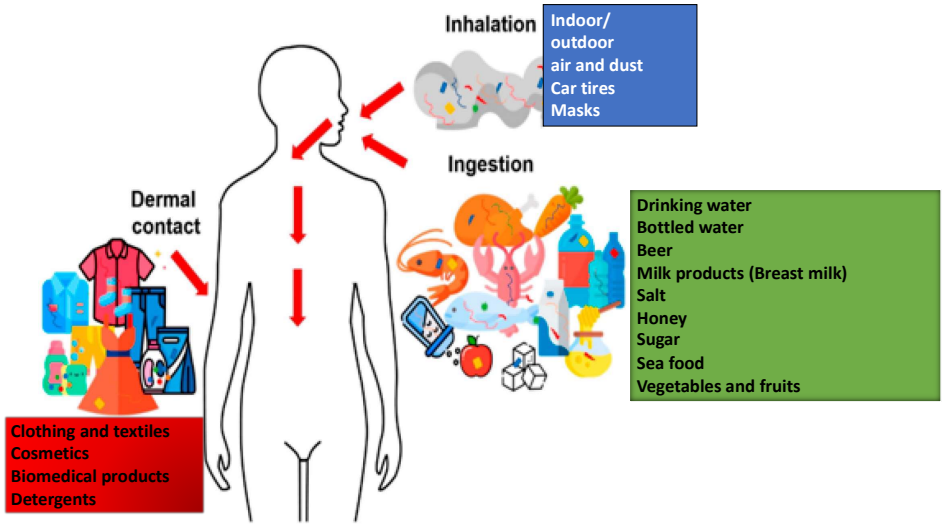

Figure 1. Human exposure to MNPLs. Human exposure to MNPLs through inhalation of indoor and outdoor air and dermal contact happens through clothing and self-applied cosmetics, but also biomedical products. In humans, exposure mainly occurs through ingestion of contaminated food and water. Neonates and infants are exposed to toxic plastics through breast milk and milk substitutes, but also by chewing on plastic-polluted toys.

MNPLs have been isolated from many human tissues, including stool [68], blood (even after a single oral exposure [69]), lung [70,71], breast milk and formula [66], and colon [72,73]. Contaminated vascular tissues allow microplastic transportation to human tissues [74], and evidence confirms that ultrafine plastics cross the blood–brain barrier (BBB) [75]. During exposure, non-plastic particles acquire an environmental eco-corona consisting of biomolecules, organic matter, and chemical and biological contaminants [52]. These accumulate on the surface of plastic particles when they are exposed to biological fluids [76,77] and the protein–plastic interaction enables passage through the BBB [78]. Alternatively, MNPLs may penetrate the brain directly through the nasal olfactory pathway. This route has been shown to cause neurotoxicity in animal models such as marine invertebrates, fish, and rodents [9,79]. Some small-sized polystyrene nanoplastics can enter neurons by endocytosis and accumulate in the cytoplasm [80].

6. Neuroinflammation and MNPLs

Chronic inflammation is a key feature in the pathogenesis of ALS, and other neurodegenerative diseases [81,82], and is the principal toxic response to MNPLs in all tissues studied [83–85]. After absorption, their interaction with neurons and glia is dependent on their surface properties and the biological molecules they encounter, including carbohydrates, proteins, and phospholipids, and they form a 'crown' called a protein corona [20]. In vitro studies indicate that polystyrene nanoparticles coated with a protein corona facil-

itate translocation and may alter its form and characteristics, potentially increasing cell interactions and toxicity [86].

Due to their post-mitotic nature, and inability to regenerate, neurons may be more vulnerable to cellular toxicity and are more ATP-dependent than other cells, making them more susceptible to energy crises associated with inflammation [87]. The neuroinflammatory cascade is activated by microglia and astrocytes and mediated by key pro-inflammatory cytokines (IL-1β, IL-6, and TNFα), which regulate adhesion molecule expression, cell growth, cell division, and apoptosis [88]. The response is further mediated by extracellular signaling chemokines (CCL2, CCL5, CXCL1), secondary messengers (nitric oxide and prostaglandins), and reactive oxygen species (ROS) [89].

Despite extensive recognition of plastic particles in most human tissues, studies exploring the inflammatory response to toxicity have largely relied on assumptions from animal models or in vitro cell culture models [9,20,40]. In vitro experiments with a human brain-derived microglial cell line (HMC-3) exposed to secondary (weathered) MNPLs demonstrated a severe inflammatory response [90], but the extent of neurotoxic outcomes has been limited by lack of comparison to different particle types, shapes, sizes, and exposure concentrations [51,83]. In aquatic species, MNPL neurotoxicity induces a classic inflammatory response with increased pro-inflammatory cytokine production, oxidative stress with generation of ROS, and mitochondrial dysfunction [91]. Neurotransmitter systems, including glutamate, GABA serotonin, histamine, and ATP are also impaired [10,92], and these are known to mediate pathophysiological functions of microglia in ALS [93].

7. MNPL Neonatal Toxicity

The abnormal biological cascades that culminate in ALS predate the clinical disease by years or decades [94], and it has been hypothesized that the seeds for sporadic ALS may evolve as early as the neonatal period [95]. The neonatal and perinatal periods engender complex neuronal activity, intense neurogenesis, establishment of neuronal circuitry, and cell migration with neuronal differentiation and sprouting of axonal connections [95]. Even small doses of MNPLs can impact these processes, setting the stage for neurodegenerative disorders in later life [64,96]. The corticomotoneuronal system, key in the pathogenesis of ALS [97], because of its large Betz multi-synaptic neurons, is particularly vulnerable to toxicity during development [98].

Neonates are continuously exposed to MNPLs through everyday items such as breast milk, cow milk, and infant milk powder, as well as plastic-based products like feeding bottles and breast milk storage bags [99]. Studies of human stool, fetus, and placenta provide direct evidence of exposure to MNPLs in infants and children [100], and they are detectable in breast and human milk substitutes [66]. MNPLs have been identified in amniotic fluid during pregnancy [101]. A recent high-resolution ex vivo MRI study in mice revealed brain abnormalities, including in the motor cortex and corpus callosum (both predominantly involved in ALS), following maternal exposure to polystyrene nanoplastics [102]. Overall there is mounting evidence that exposure to MNPLs is detrimental during the perinatal period, particularly through ingestion, and can cause toxicity specifically in primary motor neurons by activating an oxidative stress response and inducing apoptosis, consequently impairing motor performance [103].

During embryonic and neonatal periods, epigenetic mechanisms are responsible for shaping early developmental programming of the central nervous system, which is particularly sensitive to a toxic environment. Epigenetics maintains the memory of a phenotype chromosome without alterations in the DNA sequence, bridging environmental stimuli and gene expression and environmental exposure to toxins such as nanoplastics. Epigenetic modification fine tunes gene expression in response to changes in the environment. The alterations result in chromatin remodeling, direct covalent modifications to the DNA itself, post-translational modifications to histone proteins, and activity of noncoding RNAs [104]. Normally, DNA and histone modifications are erased and re-established in each generation through a developmental reprogramming, and lifetime epigenetic changes are not

generally inherited by subsequent generations. However, there is evidence that at least some epigenetic alterations can escape re-establishment of the epigenome with alterations in the epigenetic profile occurring in the offspring of exposed individuals indicative of intergenerational inheritance [105,106]. Further investigation is required to determine the specificity of MNPLs in relation to epigenic modifications.

8. The Gut–Brain Axis and MNPLs

In humans, oral ingestion is the prime means of exposure to MNPLs, and the gastrointestinal tract constantly interacts with these small particles [107]. Micro/nano plastics induce inflammation in the gastrointestinal system, promoting dysbiosis of the gut microbiome [83,84]. An abnormal gut microbiome and the gut–brain axis have been implicated in the pathogenesis of all major neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, Huntington's disease, and ALS) [108,109]. Gut dysbiosis in ALS was initially reported in 2015 [110], and over the past decade, further reports have described an impaired gut microbiome in ALS patients and rodent models [23–25,111–113].

The gut–brain axis is a bidirectional network [114,115]. Communications between the gut microbiome and the central nervous system are multifaceted involving the vagus nerve, which transmits neural signals from the brain to the gut, vasculature, immunological, lymphatic and glymphatic systems, and the hypothalamic–pituitary–adrenal axis. The gut microbes and their metabolites and the gut neurotransmitters and hormones secreted by enteroendocrine cells can be transported to the brain, interacting with the host immune system. They include glutamate, dopamine, and acetylcholine, and inhibitory γ-aminobutyric acid (GABA). There are also intermediate compounds, notably short chain fatty acids and tryptophan [116]. Signals generated by these neurotransmitters and molecules are transported to the brain via vagus nerve afferents [114,117]. In response, the brain signals back to enterochromaffin cells and enteroendocrine cells in the gut wall, and the mucosal immune system via vagus efferents (See Figure 2).

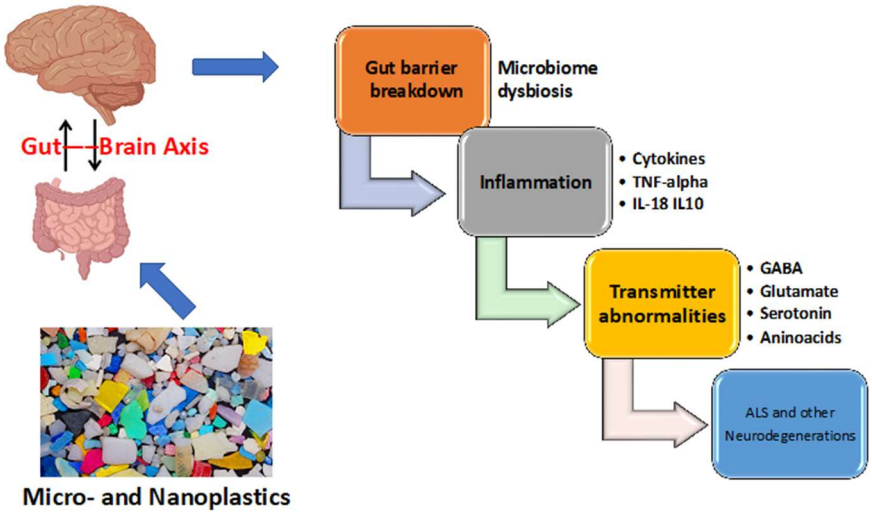

Figure 2. MNPLs and the gut–brain axis: Ingestion is the prime entry route of MNPLs in humans. These pollutants break the gut barrier, cause microbiome dysbiosis and then induce an inflammatory reaction which may be chronic. Impairment of the gut–brain axis is implicated in the pathogenesis of ALS.

Gut microbe-derived metabolites traverse the gut barrier and activate innate immune cells, with an increase of proinflammatory cytokines (TNF-α, IL-1β, IL-6, amongst others) inducing subsequent neuroinflammation. The same metabolites can traverse an impaired blood–brain barrier and interact with microglia in the brain, exacerbating neuroinflammation [118].

MNPLs can directly break through the gut barrier. The inner mucus layer of the gut acts as a barrier protecting the underlying epithelial cells from toxicants including

MNPLs. When they reach the inner mucus layer, they induce development of biofilms with complex bacterial communities, which subsequently degrade its integrity and penetrate the epithelial barrier [119]. There is limited human information regarding this, but animal studies confirm that exposure to MNPLs causes oxidative damage and inflammation and immune cell toxicity in the gut, with destruction of the gut epithelium [120]. As a result, MNPLs can translocate to secondary structures, including the brain [121]. Several species develop nanoplastic-induced gut dysbiosis with health impacts [21]. This occurs in zebrafish [122–124], crayfish [125], and mice [126–128], and exposure to polyethylene microplastics also affects the immature human and non-human gut microbiome [129,130]. The gut microbiome influences neurodevelopment and when impaired can cause neurodevelopmental disorders [131,132].

As discussed further below, truncation, abnormal aggregation and mislocalization to the cytoplasm of TDP-43 encoded by the *TARDBP* gene, an RNA-binding protein that predominantly localizes to the nucleus, are hallmarks of ALS pathology [133]. Aggregates of TDP-43 are considered causative of ALS and frontotemporal dementia. When TDP-43 becomes mutated or mislocalized out of the nucleus of neurons and glial cells and forms cytoplasmic inclusions, it can lead to RNA splicing dysregulation. This in turn can result in the generation of an altered transcriptome and proteome within the neuron, changing the diversity and quantity of gene products. In the early stages of ALS, soluble cytoplasmic TDP-43 is found in the large pyramidal neurons, including Betz cells within the motor cortex [98]. This toxic TDP-43 subsequently spreads to bulbar and spinal motoneurons with TDP-43 aggregate formation [134].

Recent evidence indicates TDP-43 aggregates occur in several non-central nervous tissues, particularly human gastrointestinal tissue, observed as part of routine clinical practice among ALS patients prior to diagnosis of their motor symptoms [135]. It is unlikely that TDP-43 aggregates in the gut are pathogenic but they may well mirror a similar long preclinical accumulation in the brain. It is unclear if TDP-43 aggregates in the gut are relevant in the breakdown of the gut barrier, dysbiosis, and impairment of the gut–brain axis.

9. Pathways to ALS from MNPLs

Key pathogenic elements of ALS are mislocalization and aggregation of the DNA/RNA-binding protein TDP-43 [136], cortical hyperexcitability [137,138], and neuroinflammation [139–141]. Figure 3 depicts how these may interact in response to MNPL neurotoxicity. TDP-43 is an essential protein involved in several DNA and RNA processing events, including gene transcription, pre-RNA splicing, RNA translation and degradation, and critical for normal neuronal health. Although it mainly localizes in the nucleus, TDP-43 also shuttles between the nucleus and cytoplasm for various physiologic functions. Under stress conditions, such as those induced by MNPLs, it is initially transiently recruited into membrane-less stress granules in the cytoplasm [142]. There is a mechanistic link between stress granule formation and development of pathological TPP-43 inclusions [143]. Even small changes in TDP-43 levels and its intracellular localization are highly predictive of neurodegeneration [144]. Loss of TDP-43 cryptic splicing repression occurs early in disease progression and is detectable pre-symptomatically [145]. TDP-43 CSF concentrations have been positively correlated with nanoplastics [146,147]. Inflammatory-mediated oxidative stress is a ubiquitous response to MNPL-induced inflammation, and even small doses are toxic when exposure is chronic [9].

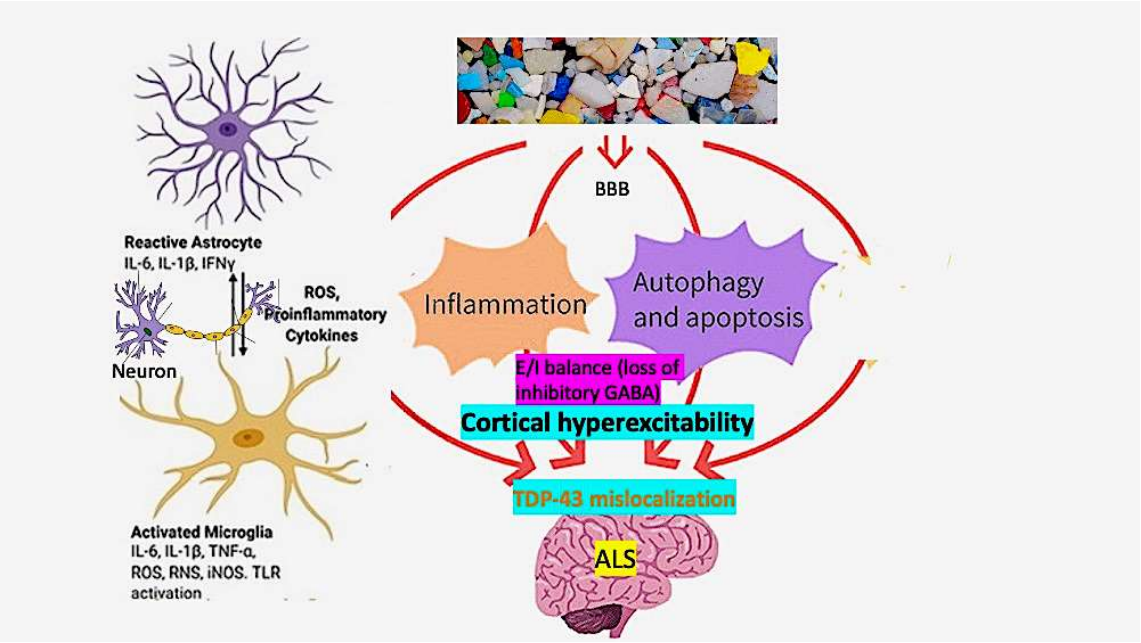

Figure 3. A route from micro/nanoplastic pollution to ALS: In non-human species, MNPLs induce a neuroinflammatory cascade involving activated microglia and astrocytes with mediation of key pro-inflammatory cytokines (IL-1β, IL-6, and TNFα) and oxidative stress to induce stress granules, with mislocalization of TDP-43 and aggregate formation. Neurotransmitter anomalies develop in favor of GABAergic inhibition and impaired excitatory/inhibitory (E/I) balance with a net increase in cortical excitability. The process is likely chronic and may commence in early years of life. These events, especially neuroinflammation, are common to all neurodegenerations.

MNPLs are known to induce neuronal excitotoxicity [148]. For example, polystyrene nanoplastics induce neuroexcitation in zebrafish larvae [149]. In a *C. elegans* model, weathered nanoplastics significantly reduced both glutamate and GABA transmitter function, but GABA to a greater extent [150]. Disrupted GABAergic circuits shift the balance between cortical excitation and inhibition (excitatory/inhibitory balance), a crucial aspect for normal brain function [151], and more specifically finely tuned motor function mediated by monosynaptic corticomotoneuronal projections [152].

Evidence from human electrophysiological studies and ALS animal models strongly supports cortical hyperexcitability as important in the pathogenesis of ALS, occurring prior to the onset of the clinical syndrome [138,153]. There is a clear link between cortical hyperexcitability and subsequent downstream degeneration and loss of anterior horn cells [154,155]. Cortical hyperexcitability is a combined consequence of increased excitatory (glutamatergic) inputs to the upper motor neuron, paralleled by decreased inhibition mediated through GABAergic interneurons. Evidence from human transcranial magnetic stimulation studies indicates decreased GABAergic inhibition plays the dominant role in cortical excitability [156]. $GABA_A$ receptors in the motor cortex of patients with ALS show downregulated α1-subunit and upregulated β1-subunit mRNAs indicating altered receptor function [157]. The resulting imbalance in excitation/inhibition is shared by other neurodegenerative diseases [158,159], and may be an early sign leading to disease in later years [95]. Studies in *C. elegans* indicate that glutamate and especially GABA are significantly reduced after administration of weathered microplastics [150,160], resulting in net excitotoxicity.

10. Preventive and Therapeutic Measures

Plastic control strategies are being vigorously explored and are becoming effective for mitigating plastic pollution and its impact on the environment ([11] and https://www.nih.

gov/news-events/news-releases/microplastics-algal-blooms-seafood-safety-are-public-health-concerns-addressed-new-oceans-human-health-centers 16 April 2024). Single-use products made of polymeric plastics (drinking bottles, straws, cutlery, coffee cups, and bags), are recognized as a significant source of plastic pollution, and there is increasing legislation preventing their use. However, some plastic materials, for example facemasks, prominently used during the coronavirus epidemic (COVID-19), are challenging to recycle. Using biodegradable plastics and changing individual behaviours has its own challenges, making it important to ensure that all aspects of microplastic issues, including their origins, types, effects, and fates, are widely publicized. Of concern is MNPL toxicity occurring during the neonatal period, setting the stage for later life neurodegeneration, as well as multigenerational epigenic influences. Our focus needs to be on strategies for their successful removal from air and aquatic ecosystems. These include coagulation, membrane bioreactor technology, rapid sand filtration, and adsorption, in addition to more innovative techniques such as electrocoagulation, photocatalytic degradation, electrochemical oxidation, and magnetic separation [11].

Ingestion is the prime source of plastic toxicity in humans, resulting in gut dysbiosis as an early step. Adopting a diet rich in fiber, whole grains, fruits, and vegetables can promote the growth of beneficial bacteria in the gut, along with avoiding processed foods. Probiotics help restore balance to the gut microbiota and because prebiotics are non-digestible fibers, they enhance beneficial bacteria in the gut [118]. More specifically, the prebiotic role of polyphenols influences gut microbiota in neurodegenerative disorders by modulating intracellular signaling pathways. Metabolites of polyphenols function directly as neurotransmitters by crossing the blood–brain barrier [161]. Another approach is use of fecal microbial transplantation, which aims to restore eubiosis, rebalance gut microbiota, and reestablish immunological tolerance. A recent double-blind, controlled, multicenter study using fecal microbial transplantation in ALS was found to modulate neuroinflammation, modifying disease activity and progression [162].

The glymphatic system and the meningeal lymphatic vessels provide a pathway for transport of solutes and clearance of toxic material from the brain [163]. Impairment of this system has been implicated in several neurodegenerations in association with pollutants [164]. Of specific relevance to ALS, this is applicable to TDP-43 and glutamate, both major elements in disease pathogenesis. The glymphatic system clears metabolic waste in the brain by exchanging the interstitial fluid (ISF) surrounding neurons with 'clean' cerebrospinal fluid (CSF) [165]. Clearance includes removal of toxic proteinaceous aggregates including TDP-43 [166], and recent studies show that neurons actively drive glymphatic clearance of waste [165]. There is an important role for glymphatic dysfunction in ALS pathology, which correlates with sleep disturbances in early-stage ALS [167]. MNPLs may impair glymphatic functioning directly or indirectly and there are strategies directed at improving glymphatic clearance, which may also reduce MNPL-induced neurotoxicity [168].

11. Conclusions

Neurotoxicity and other health hazards related to the exponential growth of MNPLs are new. MNPL-related human health hazards are becoming recognized but information has been largely derived from non-human species. MNPLs, especially when weathered, can breach the BBB or access the brain through nose-to-brain translocation. However, studies in ALS specifically related to MNPL toxicity have not been reported and there have been no neuropathological studies, or reports of specific biomarkers related to microplastics or nanoplastics in ALS. The exposome, referred to earlier in this review, integrates external exposures arising from the outside milieu, their biological fingerprints in biofluids, and susceptibility factors that modulate biological responses to the environment. New advances in exposomics in neurodegeneration will enhance our knowledge of the toxicological effects of MNPLs in ALS [163]. The resulting neurotoxicity is reflected in an inflammatory response with intracytoplasmic stress granule formation and subsequent formation of

TDP-43 aggregates, a hallmark of ALS. Neurotransmitter anomalies involving glutamate and GABA, primarily shown in non-human species, result in altered excitation/inhibition balance, favoring loss of inhibition. This induces cortical hyperexcitability, another important pathogenic mechanism in ALS. In humans, ingestion is the commonest route of exposure to MNPLs, and causes acute and chronic gut inflammation with breakdown of the gut barrier. Resulting dysbiosis of the gut microbiome with disruption of the gut–brain axis is implicated in neurodegenerative diseases, including ALS. There is significant potential for exposure to MNPLs during the neonatal and early childhood periods through breast milk, milk substitutes, and toys. The low-grade chronic neurotoxicity this induces may set the stage for later life disease including neurodegeneration. Exposure to MNPLs should be considered a risk factor for ALS and other neurodegenerative diseases.

Author Contributions: All authors contributed equally to the conceptualization, preparation, and writing of this review. All authors have read and agreed to the published version of the manuscript.

Funding: Stephen Goutman: NINDS R01NS120926, CDC/ATSDR R01TS000344, CDC/ATSDR R01TS000327, NINDS R01NS127188, NIEHS R01ES030049.

Data Availability Statement: No new data were created or analyzed in the preparation of this review. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Feldman, E.L.; Goutman, S.A.; Petri, S.; Mazzini, L.; Savelieff, M.G.; Shaw, P.J.; Sobue, G. Amyotrophic lateral sclerosis. *Lancet* **2022**, *400*, 1363–1380. [CrossRef] [PubMed]
2. Kiernan, M.C.; Vucic, S.; Cheah, B.C.; Turner, M.R.; Eisen, A.; Hardiman, O.; Burrell, J.R.; Zoing, M.C. Amyotrophic lateral sclerosis. *Lancet* **2011**, *377*, 942–955. [CrossRef] [PubMed]
3. Goutman, S.A.; Hardiman, O.; Al-Chalabi, A.; Chio, A.; Savelieff, M.G.; Kiernan, M.C.; Feldman, E.L. Emerging insights into the complex genetics and pathophysiology of amyotrophic lateral sclerosis. *Lancet Neurol.* **2022**, *21*, 465–479. [CrossRef] [PubMed]
4. Tam, O.H.; Rozhkov, N.V.; Shaw, R.; Kim, D.; Hubbard, I.; Fennessey, S.; Propp, N.; Consortium, N.A.; Fagegaltier, D.; Harris, B.T.; et al. Postmortem Cortex Samples Identify Distinct Molecular Subtypes of ALS: Retrotransposon Activation, Oxidative Stress, and Activated Glia. *Cell Rep.* **2019**, *29*, 1164–1177.e1165. [CrossRef] [PubMed]
5. Dou, J.; Bakulski, K.; Guo, K.; Hur, J.; Zhao, L.; Saez-Atienzar, S.; Stark, A.; Chia, R.; Garcia-Redondo, A.; Rojas-Garcia, R.; et al. Cumulative Genetic Score and C9orf72 Repeat Status Independently Contribute to Amyotrophic Lateral Sclerosis Risk in 2 Case-Control Studies. *Neurol. Genet.* **2023**, *9*, e200079. [CrossRef] [PubMed]
6. Goutman, S.A.; Savelieff, M.G.; Jang, D.G.; Hur, J.; Feldman, E.L. The amyotrophic lateral sclerosis exposome: Recent advances and future directions. *Nat. Rev. Neurol.* **2023**, *19*, 617–634. [CrossRef] [PubMed]
7. Benatar, M.; Goutman, S.A.; Staats, K.A.; Feldman, E.L.; Weisskopf, M.; Talbott, E.; Dave, K.D.; Thakur, N.M.; Al-Chalabi, A. A roadmap to ALS prevention: Strategies and priorities. *J. Neurol. Neurosurg. Psychiatry* **2023**, *94*, 399–402. [CrossRef]
8. Sakowski, S.A.; Koubek, E.J.; Chen, K.S.; Goutman, S.A.; Feldman, E.L. Role of the Exposome in Neurodegenerative Disease: Recent Insights and Future Directions. *Ann. Neurol.* **2024**, *95*, 635–652. [CrossRef]
9. Prust, M.; Meijer, J.; Westerink, R.H.S. The plastic brain: Neurotoxicity of micro- and nanoplastics. *Part. Fibre Toxicol.* **2020**, *17*, 24. [CrossRef]
10. Chen, H.; Hua, X.; Yang, Y.; Wang, C.; Jin, L.; Dong, C.; Chang, Z.; Ding, P.; Xiang, M.; Li, H.; et al. Chronic exposure to UV-aged microplastics induces neurotoxicity by affecting dopamine, glutamate, and serotonin neurotransmission in *Caenorhabditis elegans*. *J. Hazard. Mater.* **2021**, *419*, 126482. [CrossRef]
11. Osman, A.I.; Hosny, M.; Eltaweil, A.S.; Omar, S.; Elgarahy, A.M.; Farghali, M.; Yap, P.S.; Wu, Y.S.; Nagandran, S.; Batumalaie, K.; et al. Microplastic sources, formation, toxicity and remediation: A review. *Environ. Chem. Lett.* **2023**, *21*, 2129–2169. [CrossRef]
12. Paez-Colasante, X.; Figueroa-Romero, C.; Sakowski, S.A.; Goutman, S.A.; Feldman, E.L. Amyotrophic lateral sclerosis: Mechanisms and therapeutics in the epigenomic era. *Nat. Rev. Neurol.* **2015**, *11*, 266–279. [CrossRef] [PubMed]
13. Ijomone, O.M.; Ijomone, O.K.; Iroegbu, J.D.; Ifenatuoha, C.W.; Olung, N.F.; Aschner, M. Epigenetic influence of environmentally neurotoxic metals. *Neurotoxicology* **2020**, *81*, 51–65. [CrossRef] [PubMed]
14. Bennett, S.A.; Tanaz, R.; Cobos, S.N.; Torrente, M.P. Epigenetics in amyotrophic lateral sclerosis: A role for histone post-translational modifications in neurodegenerative disease. *Transl. Res.* **2019**, *204*, 19–30. [CrossRef]
15. Hur, J.; Paez-Colasante, X.; Figueroa-Romero, C.; Lo, T.W.; Barmada, S.J.; Paulsen, M.T.; Ljungman, M.; Alakwaa, F.M.; Savelieff, M.G.; Goutman, S.A.; et al. miRNA analysis reveals novel dysregulated pathways in amyotrophic lateral sclerosis. *Hum. Mol. Genet.* **2023**, *32*, 934–947. [CrossRef] [PubMed]

16. Liu, Z.; Qiang, Y.; Shan, S.; Wang, S.; Song, F. Carbon disulfide induces accumulation of TDP-43 in the cytoplasm and mitochondrial dysfunction in rat spinal cords. *Cereb. Cortex* **2024**, *32*, bhad526. [CrossRef]
17. Ostle, C.; Thompson, R.C.; Broughton, D.; Gregory, L.; Wootton, M.; Johns, D.G. The rise in ocean plastics evidenced from a 60-year time series. *Nat. Commun.* **2019**, *10*, 1622. [CrossRef]
18. Ward, C.P.; Reddy, C.M.; Edwards, B.; Perri, S.T. To curb plastic pollution, industry and academia must unite. *Nature* **2024**, *625*, 658–662. [CrossRef]
19. Thompson, R.C.; Olsen, Y.; Mitchell, R.P.; Davis, A.; Rowland, S.J.; John, A.W.; McGonigle, D.; Russell, A.E. Lost at sea: Where is all the plastic? *Science* **2004**, *304*, 838. [CrossRef]
20. Ali, N.; Katsouli, J.; Marczylo, E.L.; Gant, T.W.; Wright, S.; Bernardino de la Serna, J. The potential impacts of micro-and-nano plastics on various organ systems in humans. *EBioMedicine* **2024**, *99*, 104901. [CrossRef]
21. Fackelmann, G.; Sommer, S. Microplastics and the gut microbiome: How chronically exposed species may suffer from gut dysbiosis. *Mar. Pollut. Bull.* **2019**, *143*, 193–203. [CrossRef] [PubMed]
22. Grodzicki, W.; Dziendzikowska, K.; Gromadzka-Ostrowska, J.; Kruszewski, M. Nanoplastic Impact on the Gut-Brain Axis: Current Knowledge and Future Directions. *Int. J. Mol. Sci.* **2021**, *22*, 2795. [CrossRef]
23. Martin, S.; Battistini, C.; Sun, J. A Gut Feeling in Amyotrophic Lateral Sclerosis: Microbiome of Mice and Men. *Front. Cell Infect. Microbiol.* **2022**, *12*, 839526. [CrossRef] [PubMed]
24. Zeng, Q.; Shen, J.; Chen, K.; Zhou, J.; Liao, Q.; Lu, K.; Yuan, J.; Bi, F. The alteration of gut microbiome and metabolism in amyotrophic lateral sclerosis patients. *Sci. Rep.* **2020**, *10*, 12998. [CrossRef]
25. Boddy, S.L.; Giovannelli, I.; Sassani, M.; Cooper-Knock, J.; Snyder, M.P.; Segal, E.; Elinav, E.; Barker, L.A.; Shaw, P.J.; McDermott, C.J. The gut microbiome: A key player in the complexity of amyotrophic lateral sclerosis (ALS). *BMC Med.* **2021**, *19*, 13. [CrossRef]
26. Wild, C.P. Complementing the genome with an "exposome": The outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol. Biomark. Prev.* **2005**, *14*, 1847–1850. [CrossRef]
27. Vineis, P.; Schulte, P.; McMichael, A.J. Misconceptions about the use of genetic tests in populations. *Lancet* **2001**, *357*, 709–712. [CrossRef]
28. Tamiz, A.P.; Koroshetz, W.J.; Dhruv, N.T.; Jett, D.A. A focus on the neural exposome. *Neuron* **2022**, *110*, 1286–1289. [CrossRef] [PubMed]
29. Goutman, S.A.; Boss, J.; Jang, D.G.; Mukherjee, B.; Richardson, R.J.; Batterman, S.; Feldman, E.L. Environmental risk scores of persistent organic pollutants associate with higher ALS risk and shorter survival in a new Michigan case/control cohort. *J. Neurol. Neurosurg. Psychiatry* **2024**, *95*, 241–248. [CrossRef]
30. Jang, D.G.; Dou, J.; Koubek, E.J.; Teener, S.; Zhao, L.; Bakulski, K.M.; Mukherjee, B.; Batterman, S.A.; Feldman, E.L.; Goutman, S.A. Metal mixtures associate with higher amyotrophic lateral sclerosis risk and mortality independent of genetic risk and correlate to self-reported exposures: A case-control study. *medRxiv* **2024**. [CrossRef]
31. Goutman, S.A.; Boss, J.; Patterson, A.; Mukherjee, B.; Batterman, S.; Feldman, E.L. High plasma concentrations of organic pollutants negatively impact survival in amyotrophic lateral sclerosis. *J. Neurol. Neurosurg. Psychiatry* **2019**, *90*, 907–912. [CrossRef] [PubMed]
32. Vermeulen, R.; Schymanski, E.L.; Barabasi, A.L.; Miller, G.W. The exposome and health: Where chemistry meets biology. *Science* **2020**, *367*, 392–396. [CrossRef]
33. Frias, J.; Nash, R. Microplastics: Finding a consensus on the definition. *Mar. Pollut. Bull.* **2019**, *138*, 145–147. [CrossRef] [PubMed]
34. Weis, J.S.; Alava, J.J. (Micro)Plastics Are Toxic Pollutants. *Toxics* **2023**, *11*, 935. [CrossRef] [PubMed]
35. Duan, J.; Bolan, N.; Li, Y.; Ding, S.; Atugoda, T.; Vithanage, M.; Sarkar, B.; Tsang, D.C.W.; Kirkham, M.B. Weathering of microplastics and interaction with other coexisting constituents in terrestrial and aquatic environments. *Water Res.* **2021**, *196*, 117011. [CrossRef] [PubMed]
36. Arp, H.P.H.; Kuhnel, D.; Rummel, C.; MacLeod, M.; Potthoff, A.; Reichelt, S.; Rojo-Nieto, E.; Schmitt-Jansen, M.; Sonnenberg, J.; Toorman, E.; et al. Weathering Plastics as a Planetary Boundary Threat: Exposure, Fate, and Hazards. *Environ. Sci. Technol.* **2021**, *55*, 7246–7255. [CrossRef] [PubMed]
37. Sobhani, Z.; Lei, Y.; Tang, Y.; Wu, L.; Zhang, X.; Naidu, R.; Megharaj, M.; Fang, C. Microplastics generated when opening plastic packaging. *Sci. Rep.* **2020**, *10*, 4841. [CrossRef] [PubMed]
38. Andrady, A.L.; Neal, M.A. Applications and societal benefits of plastics. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2009**, *364*, 1977–1984. [CrossRef] [PubMed]
39. Andrady, A.L. The plastic in microplastics: A review. *Mar. Pollut. Bull.* **2017**, *119*, 12–22. [CrossRef]
40. Campanale, C.; Massarelli, C.; Savino, I.; Locaputo, V.; Uricchio, V.F. A Detailed Review Study on Potential Effects of Microplastics and Additives of Concern on Human Health. *Int. J. Environ. Res. Public. Health* **2020**, *17*, 1212. [CrossRef]
41. Xu, J.L.; Lin, X.; Wang, J.J.; Gowen, A.A. A review of potential human health impacts of micro- and nanoplastics exposure. *Sci. Total Environ.* **2022**, *851*, 158111. [CrossRef] [PubMed]
42. Yee, M.S.; Hii, L.W.; Looi, C.K.; Lim, W.M.; Wong, S.F.; Kok, Y.Y.; Tan, B.K.; Wong, C.Y.; Leong, C.O. Impact of Microplastics and Nanoplastics on Human Health. *Nanomaterials* **2021**, *11*, 496. [CrossRef] [PubMed]
43. Rodrigues, A.C.B.; de Jesus, G.P.; Waked, D.; Gomes, G.L.; Silva, T.M.; Yariwake, V.Y.; da Silva, M.P.; Magaldi, A.J.; Veras, M.M. Scientific Evidence about the Risks of Micro and Nanoplastics (MNPLs) to Human Health and Their Exposure Routes through the Environment. *Toxics* **2022**, *10*, 308. [CrossRef] [PubMed]

44. Qi, R.; Jones, D.L.; Li, Z.; Liu, Q.; Yan, C. Behavior of microplastics and plastic film residues in the soil environment: A critical review. *Sci. Total Environ.* **2020**, *703*, 134722. [CrossRef] [PubMed]
45. Enyoh, C.E.; Verla, A.W.; Verla, E.N.; Ibe, F.C.; Amaobi, C.E. Airborne microplastics: A review study on method for analysis, occurrence, movement and risks. *Environ. Monit. Assess.* **2019**, *191*, 668. [CrossRef] [PubMed]
46. Jambeck, J.R.; Geyer, R.; Wilcox, C.; Siegler, T.R.; Perryman, M.; Andrady, A.; Narayan, R.; Law, K.L. Marine pollution. Plastic waste inputs from land into the ocean. *Science* **2015**, *347*, 768–771. [CrossRef]
47. Prata, J.C.; da Costa, J.P.; Lopes, I.; Duarte, A.C.; Rocha-Santos, T. Environmental exposure to microplastics: An overview on possible human health effects. *Sci. Total Environ.* **2020**, *702*, 134455. [CrossRef] [PubMed]
48. Borrelle, S.B.; Ringma, J.; Law, K.L.; Monnahan, C.C.; Lebreton, L.; McGivern, A.; Murphy, E.; Jambeck, J.; Leonard, G.H.; Hilleary, M.A.; et al. Predicted growth in plastic waste exceeds efforts to mitigate plastic pollution. *Science* **2020**, *369*, 1515–1518. [CrossRef] [PubMed]
49. Heyerdahl, T. Atlantic ocean pollution and biota observed by the "Ra" expeditions. *Biol. Conserv.* **1971**, *3*, 164–168. [CrossRef]
50. Zeb, A.; Liu, W.; Ali, N.; Shi, R.; Wang, Q.; Wang, J.; Li, J.; Yin, C.; Liu, J.; Yu, M.; et al. Microplastic pollution in terrestrial ecosystems: Global implications and sustainable solutions. *J. Hazard. Mater.* **2024**, *461*, 132636. [CrossRef]
51. Bank, M.S.; Mitrano, D.M.; Rillig, M.C.; Lin, C.S.K.; Ok, Y.S. Embrace complexity to understand microplastic pollution. *Nat. Rev. Earth Environ.* **2022**, *3*, 736–737. [CrossRef] [PubMed]
52. Vethaak, A.D.; Legler, J. Microplastics and human health. *Science* **2021**, *371*, 672–674. [CrossRef]
53. Campanale, C.; Stock, F.; Massarelli, C.; Kochleus, C.; Bagnuolo, G.; Reifferscheid, G.; Uricchio, V.F. Microplastics and their possible sources: The example of Ofanto river in southeast Italy. *Environ. Pollut.* **2020**, *258*, 113284. [CrossRef] [PubMed]
54. Reed, R. Dawn of the plasticene age. *New Sci.* **2015**, *225*, 28–32. [CrossRef]
55. Bergami, E.; Rota, E.; Caruso, T.; Birarda, G.; Vaccari, L.; Corsi, I. Plastics everywhere: First evidence of polystyrene fragments inside the common Antarctic collembolan Cryptopygus antarcticus. *Biol. Lett.* **2020**, *16*, 20200093. [CrossRef] [PubMed]
56. Rochman, C.M.; Hentschel, B.T.; Teh, S.J. Long-term sorption of metals is similar among plastic types: Implications for plastic debris in aquatic environments. *PLoS ONE* **2014**, *9*, e85433. [CrossRef]
57. Ogata, Y.; Takada, H.; Mizukawa, K.; Hirai, H.; Iwasa, S.; Endo, S.; Mato, Y.; Saha, M.; Okuda, K.; Nakashima, A.; et al. International Pellet Watch: Global monitoring of persistent organic pollutants (POPs) in coastal waters. 1. Initial phase data on PCBs, DDTs, and HCHs. *Mar. Pollut. Bull.* **2009**, *58*, 1437–1446. [CrossRef]
58. Mortensen, N.P.; Fennell, T.R.; Johnson, L.M. Unintended human ingestion of nanoplastics and small microplastics through drinking water, beverages, and food sources. *NanoImpact* **2021**, *21*, 100302. [CrossRef] [PubMed]
59. Lu, W.; Li, X.; Wang, S.; Tu, C.; Qiu, L.; Zhang, H.; Zhong, C.; Li, S.; Liu, Y.; Liu, J.; et al. New Evidence of Microplastics in the Lower Respiratory Tract: Inhalation through Smoking. *Environ. Sci. Technol.* **2023**, *57*, 8496–8505. [CrossRef]
60. Mehmood, T.; Hassan, M.A.; Faheem, M.; Shakoor, A. Why is inhalation the most discriminative route of microplastics exposure? *Environ. Sci. Pollut. Res. Int.* **2022**, *29*, 49479–49482. [CrossRef]
61. Saha, G.; Chandrasekaran, N. Isolation and characterization of microplastics from skin care products; interactions with albumin proteins and in-vivo toxicity studies on Artemia salina. *Environ. Toxicol. Pharmacol.* **2023**, *99*, 104112. [CrossRef] [PubMed]
62. Di Fiore, C.; Carriera, F.; Russo, M.V.; Avino, P. Are Microplastics a Macro Issue? A Review on the Sources of Contamination, Analytical Challenges and Impact on Human Health of Microplastics in Food. *Foods* **2023**, *12*, 3915. [CrossRef] [PubMed]
63. Zuri, G.; Karanasiou, A.; Lacorte, S. Microplastics: Human exposure assessment through air, water, and food. *Environ. Int.* **2023**, *179*, 108150. [CrossRef] [PubMed]
64. Amran, N.H.; Zaid, S.S.M.; Mokhtar, M.H.; Manaf, L.A.; Othman, S. Exposure to Microplastics during Early Developmental Stage: Review of Current Evidence. *Toxics* **2022**, *10*, 597. [CrossRef] [PubMed]
65. Masood, F. Polymeric nanoparticles for targeted drug delivery system for cancer therapy. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2016**, *60*, 569–578. [CrossRef] [PubMed]
66. Caba-Flores, M.D.; Martinez-Valenzuela, C.; Cardenas-Tueme, M.; Camacho-Morales, A. Micro problems with macro consequences: Accumulation of persistent organic pollutants and microplastics in human breast milk and in human milk substitutes. *Environ. Sci. Pollut. Res. Int.* **2023**, *30*, 95139–95154. [CrossRef] [PubMed]
67. Kaseke, T.; Lujic, T.; Cirkovic Velickovic, T. Nano- and Microplastics Migration from Plastic Food Packaging into Dairy Products: Impact on Nutrient Digestion, Absorption, and Metabolism. *Foods* **2023**, *12*, 3043. [CrossRef] [PubMed]
68. Schwabl, P.; Koppel, S.; Konigshofer, P.; Bucsics, T.; Trauner, M.; Reiberger, T.; Liebmann, B. Detection of Various Microplastics in Human Stool: A Prospective Case Series. *Ann. Intern. Med.* **2019**, *171*, 453–457. [CrossRef] [PubMed]
69. Yang, Z.S.; Bai, Y.L.; Jin, C.H.; Na, J.; Zhang, R.; Gao, Y.; Pan, G.W.; Yan, L.J.; Sun, W. Evidence on Invasion of Blood, Adipose Tissues, Nervous System and Reproductive System of Mice after a Single Oral Exposure: Nanoplastics versus Microplastics. *Biomed. Environ. Sci.* **2022**, *35*, 1025–1037. [CrossRef]
70. Jenner, L.C.; Rotchell, J.M.; Bennett, R.T.; Cowen, M.; Tentzeris, V.; Sadofsky, L.R. Detection of microplastics in human lung tissue using muFTIR spectroscopy. *Sci. Total Environ.* **2022**, *831*, 154907. [CrossRef]
71. Amato-Lourenco, L.F.; Carvalho-Oliveira, R.; Junior, G.R.; Dos Santos Galvao, L.; Ando, R.A.; Mauad, T. Presence of airborne microplastics in human lung tissue. *J. Hazard. Mater.* **2021**, *416*, 126124. [CrossRef] [PubMed]
72. Choi, Y.J.; Kim, J.E.; Lee, S.J.; Gong, J.E.; Jin, Y.J.; Seo, S.; Lee, J.H.; Hwang, D.Y. Inflammatory response in the mid colon of ICR mice treated with polystyrene microplastics for two weeks. *Lab. Anim. Res.* **2021**, *37*, 31. [CrossRef] [PubMed]

73. Sun, H.; Chen, N.; Yang, X.; Xia, Y.; Wu, D. Effects induced by polyethylene microplastics oral exposure on colon mucin release, inflammation, gut microflora composition and metabolism in mice. *Ecotoxicol. Environ. Saf.* **2021**, *220*, 112340. [CrossRef] [PubMed]
74. Rotchell, J.M.; Jenner, L.C.; Chapman, E.; Bennett, R.T.; Bolanle, I.O.; Loubani, M.; Sadofsky, L.; Palmer, T.M. Detection of microplastics in human saphenous vein tissue using muFTIR: A pilot study. *PLoS ONE* **2023**, *18*, e0280594. [CrossRef] [PubMed]
75. Shan, S.; Zhang, Y.; Zhao, H.; Zeng, T.; Zhao, X. Polystyrene nanoplastics penetrate across the blood-brain barrier and induce activation of microglia in the brain of mice. *Chemosphere* **2022**, *298*, 134261. [CrossRef] [PubMed]
76. Kopatz, V.; Wen, K.; Kovacs, T.; Keimowitz, A.S.; Pichler, V.; Widder, J.; Vethaak, A.D.; Holloczki, O.; Kenner, L. Micro- and Nanoplastics Breach the Blood-Brain Barrier (BBB): Biomolecular Corona's Role Revealed. *Nanomaterials* **2023**, *13*, 1404. [CrossRef] [PubMed]
77. Zhang, P.; Liu, Y.; Zhang, L.; Xu, M.; Gao, L.; Zhao, B. The interaction of micro/nano plastics and the environment: Effects of ecological corona on the toxicity to aquatic organisms. *Ecotoxicol. Environ. Saf.* **2022**, *243*, 113997. [CrossRef]
78. Prado, Y. Small Plastics, Big Inflammatory Problems. In *Advances in Molecular Pathology. Advances in Experimental Medicine and Biology*; Simon, F., Bernabeu, C., Eds.; Springer: Cham, Switzerland, 2023; Volume 1408, pp. 102–127.
79. Xiong, F.; Liu, J.; Xu, K.; Huang, J.; Wang, D.; Li, F.; Wang, S.; Zhang, J.; Pu, Y.; Sun, R. Microplastics induce neurotoxicity in aquatic animals at environmentally realistic concentrations: A meta-analysis. *Environ. Pollut.* **2023**, *318*, 120939. [CrossRef] [PubMed]
80. Han, S.W.; Kim, T.Y.; Bae, J.S.; Choi, J.; Ryu, K.Y. Alleviation of neurotoxicity induced by polystyrene nanoplastics by increased exocytosis from neurons. *Biochem. Biophys. Res. Commun.* **2023**, *668*, 19–26. [CrossRef]
81. Masrori, P.; Beckers, J.; Gossye, H.; Van Damme, P. The role of inflammation in neurodegeneration: Novel insights into the role of the immune system in C9orf72 HRE-mediated ALS/FTD. *Mol. Neurodegener.* **2022**, *17*, 22. [CrossRef]
82. McCauley, M.E.; Baloh, R.H. Inflammation in ALS/FTD pathogenesis. *Acta Neuropathol.* **2019**, *137*, 715–730. [CrossRef] [PubMed]
83. da Silva Brito, W.A.; Singer, D.; Miebach, L.; Saadati, F.; Wende, K.; Schmidt, A.; Bekeschus, S. Comprehensive in vitro polymer type, concentration, and size correlation analysis to microplastic toxicity and inflammation. *Sci. Total Environ.* **2023**, *854*, 158731. [CrossRef]
84. Xu, Z.; Shen, J.; Lin, L.; Chen, J.; Wang, L.; Deng, X.; Wu, X.; Lin, Z.; Zhang, Y.; Yu, R.; et al. Exposure to irregular microplastic shed from baby bottles activates the ROS/NLRP3/Caspase-1 signaling pathway, causing intestinal inflammation. *Environ. Int.* **2023**, *181*, 108296. [CrossRef]
85. Woo, J.H.; Seo, H.J.; Lee, J.Y.; Lee, I.; Jeon, K.; Kim, B.; Lee, K. Polypropylene nanoplastic exposure leads to lung inflammation through p38-mediated NF-kappaB pathway due to mitochondrial damage. *Part. Fibre Toxicol.* **2023**, *20*, 2. [CrossRef] [PubMed]
86. Nasser, F.; Lynch, I. Secreted protein eco-corona mediates uptake and impacts of polystyrene nanoparticles on Daphnia magna. *J. Proteom.* **2016**, *137*, 45–51. [CrossRef]
87. Henderson, R.D.; Kepp, K.P.; Eisen, A. ALS/FTD: Evolution, Aging, and Cellular Metabolic Exhaustion. *Front. Neurol.* **2022**, *13*, 890203. [CrossRef] [PubMed]
88. Patil, K.R.; Mahajan, U.B.; Unger, B.S.; Goyal, S.N.; Belemkar, S.; Surana, S.J.; Ojha, S.; Patil, C.R. Animal Models of Inflammation for Screening of Anti-inflammatory Drugs: Implications for the Discovery and Development of Phytopharmaceuticals. *Int. J. Mol. Sci.* **2019**, *20*, 4367. [CrossRef]
89. Norden, D.M.; Trojanowski, P.J.; Villanueva, E.; Navarro, E.; Godbout, J.P. Sequential activation of microglia and astrocyte cytokine expression precedes increased Iba-1 or GFAP immunoreactivity following systemic immune challenge. *Glia* **2016**, *64*, 300–316. [CrossRef]
90. Kim, H.Y.; Ashim, J.; Park, S.; Kim, W.; Ji, S.; Lee, S.W.; Jung, Y.R.; Jeong, S.W.; Lee, S.G.; Kim, H.C.; et al. A preliminary study about the potential risks of the UV-weathered microplastic: The proteome-level changes in the brain in response to polystyrene derived weathered microplastics. *Environ. Res.* **2023**, *233*, 116411. [CrossRef]
91. Han, S.W.; Choi, J.; Ryu, K.Y. Recent progress and future directions of the research on nanoplastic-induced neurotoxicity. *Neural Regen. Res.* **2024**, *19*, 331–335. [CrossRef]
92. Yu, Y.; Xie, D.; Yang, Y.; Tan, S.; Li, H.; Dang, Y.; Xiang, M.; Chen, H. Carboxyl-modified polystyrene microplastics induces neurotoxicity by affecting dopamine, glutamate, serotonin, and GABA neurotransmission in *Caenorhabditis elegans*. *J. Hazard. Mater.* **2023**, *445*, 130543. [CrossRef] [PubMed]
93. Volonte, C.; Amadio, S.; Fabbrizio, P.; Apolloni, S. Functional microglia neurotransmitters in amyotrophic lateral sclerosis. *Semin. Cell Dev. Biol.* **2019**, *94*, 121–128. [CrossRef] [PubMed]
94. Eisen, A.; Kiernan, M.; Mitsumoto, H.; Swash, M. Amyotrophic lateral sclerosis: A long preclinical period? *J. Neurol. Neurosurg. Psychiatry* **2014**, *85*, 1232–1238. [CrossRef] [PubMed]
95. Kiernan, M.C.; Ziemann, U.; Eisen, A. Amyotrophic lateral sclerosis: Origins traced to impaired balance between neural excitation and inhibition in the neonatal period. *Muscle Nerve* **2019**, *60*, 232–235. [CrossRef] [PubMed]
96. Bakulski, K.M.; Blostein, F.; London, S.J. Linking Prenatal Environmental Exposures to Lifetime Health with Epigenome-Wide Association Studies: State-of-the-Science Review and Future Recommendations. *Environ. Health Perspect.* **2023**, *131*, 126001. [CrossRef] [PubMed]
97. Eisen, A. The Dying Forward Hypothesis of ALS: Tracing Its History. *Brain Sci.* **2021**, *11*, 300. [CrossRef] [PubMed]
98. Nolan, M.; Scott, C.; Hof, P.R.; Ansorge, O. Betz cells of the primary motor cortex. *J. Comp. Neurol.* **2024**, *532*, e25567. [CrossRef]
99. Paul, I.; Mondal, P.; Haldar, D.; Halder, G. Beyond the cradle—Amidst microplastics and the ongoing peril during pregnancy and neonatal stages: A holistic review. *J. Hazard. Mater.* **2024**, *469*, 133963. [CrossRef] [PubMed]

100. Kannan, K.; Vimalkumar, K. A Review of Human Exposure to Microplastics and Insights Into Microplastics as Obesogens. *Front. Endocrinol.* **2021**, *12*, 724989. [CrossRef]
101. Halfar, J.; Cabanova, K.; Vavra, K.; Delongova, P.; Motyka, O.; Spacek, R.; Kukutschova, J.; Simetka, O.; Heviankova, S. Microplastics and additives in patients with preterm birth: The first evidence of their presence in both human amniotic fluid and placenta. *Chemosphere* **2023**, *343*, 140301. [CrossRef]
102. Mercer, G.V.; Harvey, N.E.; Steeves, K.L.; Schneider, C.M.; Sled, J.G.; Macgowan, C.K.; Baschat, A.A.; Kingdom, J.C.; Simpson, A.J.; Simpson, M.J.; et al. Maternal exposure to polystyrene nanoplastics alters fetal brain metabolism in mice. *Metabolomics* **2023**, *19*, 96. [CrossRef] [PubMed]
103. Cao, X.; Xie, W.; Feng, M.; Chen, J.; Zhang, J.; Luo, J.; Wang, Y. Nanoplastic Exposure Mediates Neurodevelopmental Toxicity by Activating the Oxidative Stress Response in Zebrafish (*Danio rerio*). *ACS Omega* **2024**, *9*, 16508–16518. [CrossRef] [PubMed]
104. Tuscher, J.J.; Day, J.J. Multigenerational epigenetic inheritance: One step forward, two generations back. *Neurobiol. Dis.* **2019**, *132*, 104591. [CrossRef] [PubMed]
105. Diez-Villanueva, A.; Martin, B.; Moratalla-Navarro, F.; Moron-Duran, F.D.; Galvan-Femenia, I.; Obon-Santacana, M.; Carreras, A.; de Cid, R.; Peinado, M.A.; Moreno, V. Identification of intergenerational epigenetic inheritance by whole genome DNA methylation analysis in trios. *Sci. Rep.* **2023**, *13*, 21266. [CrossRef] [PubMed]
106. Nicolella, H.D.; de Assis, S. Epigenetic Inheritance: Intergenerational Effects of Pesticides and Other Endocrine Disruptors on Cancer Development. *Int. J. Mol. Sci.* **2022**, *23*, 4671. [CrossRef] [PubMed]
107. Jimenez-Arroyo, C.; Tamargo, A.; Molinero, N.; Moreno-Arribas, M.V. The gut microbiota, a key to understanding the health implications of micro(nano)plastics and their biodegradation. *Microb. Biotechnol.* **2023**, *16*, 34–53. [CrossRef] [PubMed]
108. Rincon Orozco, B. Gut Microbiome and Brain: Scope and Perspectives. *Int. J. Psychol. Res.* **2022**, *15*, 6–9. [CrossRef] [PubMed]
109. Villavicencio-Tejo, F.; Olesen, M.A.; Navarro, L.; Calisto, N.; Iribarren, C.; Garcia, K.; Corsini, G.; Quintanilla, R.A. Gut-Brain Axis Deregulation and Its Possible Contribution to Neurodegenerative Disorders. *Neurotox. Res.* **2023**, *42*, 4. [CrossRef] [PubMed]
110. Wu, S.; Yi, J.; Zhang, Y.G.; Zhou, J.; Sun, J. Leaky intestine and impaired microbiome in an amyotrophic lateral sclerosis mouse model. *Physiol. Rep.* **2015**, *3*, e12356. [CrossRef]
111. Fournier, C.N.; Houser, M.; Tansey, M.G.; Glass, J.D.; Hertzberg, V.S. The gut microbiome and neuroinflammation in amyotrophic lateral sclerosis? Emerging clinical evidence. *Neurobiol. Dis.* **2020**, *135*, 104300. [CrossRef]
112. Hertzberg, V.S.; Singh, H.; Fournier, C.N.; Moustafa, A.; Polak, M.; Kuelbs, C.A.; Torralba, M.G.; Tansey, M.G.; Nelson, K.E.; Glass, J.D. Gut microbiome differences between amyotrophic lateral sclerosis patients and spouse controls. *Amyotroph. Lateral Scler. Front. Degener.* **2022**, *23*, 91–99. [CrossRef] [PubMed]
113. Sun, J.; Huang, T.; Debelius, J.W.; Fang, F. Gut microbiome and amyotrophic lateral sclerosis: A systematic review of current evidence. *J. Intern. Med.* **2021**, *290*, 758–788. [CrossRef]
114. Zheng, Y.; Bonfili, L.; Wei, T.; Eleuteri, A.M. Understanding the Gut-Brain Axis and Its Therapeutic Implications for Neurodegenerative Disorders. *Nutrients* **2023**, *15*, 4631. [CrossRef]
115. Sharma, M.; Prakash, J.; Yadav, P.; Srivastava, K.; Chatterjee, K. Gut-brain axis: Synergistic approach. *Ind. Psychiatry J.* **2021**, *30*, S297–S300. [CrossRef]
116. Dicks, L.M.T. Gut Bacteria and Neurotransmitters. *Microorganisms* **2022**, *10*, 1838. [CrossRef] [PubMed]
117. Benakis, C.; Martin-Gallausiaux, C.; Trezzi, J.P.; Melton, P.; Liesz, A.; Wilmes, P. The microbiome-gut-brain axis in acute and chronic brain diseases. *Curr. Opin. Neurobiol.* **2020**, *61*, 1–9. [CrossRef]
118. Ma, Y.Y.; Li, X.; Yu, J.T.; Wang, Y.J. Therapeutics for neurodegenerative diseases by targeting the gut microbiome: From bench to bedside. *Transl. Neurodegener.* **2024**, *13*, 12. [CrossRef]
119. Bhagwat, G.; Tran, T.K.A.; Lamb, D.; Senathirajah, K.; Grainge, I.; O'Connor, W.; Juhasz, A.; Palanisami, T. Biofilms Enhance the Adsorption of Toxic Contaminants on Plastic Microfibers under Environmentally Relevant Conditions. *Environ. Sci. Technol.* **2021**, *55*, 8877–8887. [CrossRef]
120. Huang, Z.; Weng, Y.; Shen, Q.; Zhao, Y.; Jin, Y. Microplastic: A potential threat to human and animal health by interfering with the intestinal barrier function and changing the intestinal microenvironment. *Sci. Total Environ.* **2021**, *785*, 147365. [CrossRef]
121. Dang, F.; Wang, Q.; Huang, Y.; Wang, Y.; Xing, B. Key knowledge gaps for One Health approach to mitigate nanoplastic risks. *Eco Environ. Health* **2022**, *1*, 11–22. [CrossRef]
122. Shi, Y.; Chen, C.; Han, Z.; Chen, K.; Wu, X.; Qiu, X. Combined exposure to microplastics and amitriptyline caused intestinal damage, oxidative stress and gut microbiota dysbiosis in zebrafish (*Danio rerio*). *Aquat. Toxicol.* **2023**, *260*, 106589. [CrossRef] [PubMed]
123. Pei, X.; Heng, X.; Chu, W. Polystyrene nano/microplastics induce microbiota dysbiosis, oxidative damage, and innate immune disruption in zebrafish. *Microb. Pathog.* **2022**, *163*, 105387. [CrossRef] [PubMed]
124. Xie, S.; Zhou, A.; Wei, T.; Li, S.; Yang, B.; Xu, G.; Zou, J. Nanoplastics Induce More Serious Microbiota Dysbiosis and Inflammation in the Gut of Adult Zebrafish than Microplastics. *Bull. Environ. Contam. Toxicol.* **2021**, *107*, 640–650. [CrossRef] [PubMed]
125. Zhang, X.; Jin, Z.; Shen, M.; Chang, Z.; Yu, G.; Wang, L.; Xia, X. Accumulation of polyethylene microplastics induces oxidative stress, microbiome dysbiosis and immunoregulation in crayfish. *Fish. Shellfish. Immunol.* **2022**, *125*, 276–284. [CrossRef] [PubMed]
126. Lin, X.; Xie, H.; Zhang, Y.; Tian, X.; Cui, L.; Shi, N.; Wang, L.; Zhao, J.; An, L.; Wang, J.; et al. The toxicity of nano polyethylene terephthalate to mice: Intestinal obstruction, growth retardant, gut microbiota dysbiosis and lipid metabolism disorders. *Food Chem. Toxicol.* **2023**, *172*, 113585. [CrossRef] [PubMed]

127. Chen, X.; Zhuang, J.; Chen, Q.; Xu, L.; Yue, X.; Qiao, D. Polyvinyl chloride microplastics induced gut barrier dysfunction, microbiota dysbiosis and metabolism disorder in adult mice. *Ecotoxicol. Environ. Saf.* **2022**, *241*, 113809. [CrossRef] [PubMed]
128. Lu, L.; Wan, Z.; Luo, T.; Fu, Z.; Jin, Y. Polystyrene microplastics induce gut microbiota dysbiosis and hepatic lipid metabolism disorder in mice. *Sci. Total Environ.* **2018**, *631–632*, 449–458. [CrossRef] [PubMed]
129. Usman, S.; Razis, A.F.A.; Shaari, K.; Azmai, M.N.A.; Saad, M.Z.; Isa, N.M.; Nazarudin, M.F. Polystyrene microplastics induce gut microbiome and metabolome changes in Javanese medaka fish (*Oryzias javanicus* Bleeker, 1854). *Toxicol. Rep.* **2022**, *9*, 1369–1379. [CrossRef] [PubMed]
130. Fournier, E.; Ratel, J.; Denis, S.; Leveque, M.; Ruiz, P.; Mazal, C.; Amiard, F.; Edely, M.; Bezirard, V.; Gaultier, E.; et al. Exposure to polyethylene microplastics alters immature gut microbiome in an infant in vitro gut model. *J. Hazard. Mater.* **2023**, *443*, 130383. [CrossRef] [PubMed]
131. Bettag, J.; Goldenberg, D.; Carter, J.; Morfin, S.; Borsotti, A.; Fox, J.; ReVeal, M.; Natrop, D.; Gosser, D.; Kolli, S.; et al. Gut Microbiota to Microglia: Microbiome Influences Neurodevelopment in the CNS. *Children* **2023**, *10*, 1767. [CrossRef]
132. Hosie, S.; Abo-Shaban, T.; Lee, C.Y.Q.; Matta, S.M.; Shindler, A.; Gore, R.; Sharna, S.S.; Herath, M.; Crack, P.J.; Franks, A.E.; et al. The Emerging Role of the Gut-Brain-Microbiota Axis in Neurodevelopmental Disorders. *Adv. Exp. Med. Biol.* **2022**, *1383*, 141–156. [CrossRef]
133. Neumann, M.; Kwong, L.K.; Lee, E.B.; Kremmer, E.; Flatley, A.; Xu, Y.; Forman, M.S.; Troost, D.; Kretzschmar, H.A.; Trojanowski, J.Q.; et al. Phosphorylation of S409/410 of TDP-43 is a consistent feature in all sporadic and familial forms of TDP-43 proteinopathies. *Acta Neuropathol.* **2009**, *117*, 137–149. [CrossRef]
134. Braak, H.; Brettschneider, J.; Ludolph, A.C.; Lee, V.M.; Trojanowski, J.Q.; Tredici, K.D. Amyotrophic lateral sclerosis—A model of corticofugal axonal spread. *Nat. Rev. Neurol.* **2013**, *9*, 708–714. [CrossRef]
135. Pattle, S.B.; O'Shaughnessy, J.; Kantelberg, O.; Rifai, O.M.; Pate, J.; Nellany, K.; Hays, N.; Arends, M.J.; Horrocks, M.H.; Waldron, F.M.; et al. pTDP-43 aggregates accumulate in non-central nervous system tissues prior to symptom onset in amyotrophic lateral sclerosis: A case series linking archival surgical biopsies with clinical phenotypic data. *J. Pathol. Clin. Res.* **2023**, *9*, 44–55. [CrossRef]
136. Neumann, M.; Sampathu, D.M.; Kwong, L.K.; Truax, A.C.; Micsenyi, M.C.; Chou, T.T.; Bruce, J.; Schuck, T.; Grossman, M.; Clark, C.M.; et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* **2006**, *314*, 130–133. [CrossRef]
137. Vucic, S.; Kiernan, M.C. Novel threshold tracking techniques suggest that cortical hyperexcitability is an early feature of motor neuron disease. *Brain* **2006**, *129*, 2436–2446. [CrossRef]
138. Vucic, S.; Pavey, N.; Haidar, M.; Turner, B.J.; Kiernan, M.C. Cortical hyperexcitability: Diagnostic and pathogenic biomarker of ALS. *Neurosci. Lett.* **2021**, *759*, 136039. [CrossRef]
139. Swash, M. Chitinases, neuroinflammation and biomarkers in ALS. *J. Neurol. Neurosurg. Psychiatry* **2020**, *91*, 338. [CrossRef]
140. Arnoux, A.; Dupuis, L. Linking neuroinflammation to motor neuron degeneration in ALS: The critical role of CXCL13/CXCR5. *EBioMedicine* **2021**, *63*, 103149. [CrossRef]
141. Giri, P.M.; Banerjee, A.; Ghosal, A.; Layek, B. Neuroinflammation in Neurodegenerative Disorders: Current Knowledge and Therapeutic Implications. *Int. J. Mol. Sci.* **2024**, *25*, 3995. [CrossRef]
142. Ratti, A.; Gumina, V.; Lenzi, P.; Bossolasco, P.; Fulceri, F.; Volpe, C.; Bardelli, D.; Pregnolato, F.; Maraschi, A.; Fornai, F.; et al. Chronic stress induces formation of stress granules and pathological TDP-43 aggregates in human ALS fibroblasts and iPSC-motoneurons. *Neurobiol. Dis.* **2020**, *145*, 105051. [CrossRef]
143. Ueda, T.; Takeuchi, T.; Fujikake, N.; Suzuki, M.; Minakawa, E.N.; Ueyama, M.; Fujino, Y.; Kimura, N.; Nagano, S.; Yokoseki, A.; et al. Dysregulation of stress granule dynamics by DCTN1 deficiency exacerbates TDP-43 pathology in Drosophila models of ALS/FTD. *Acta Neuropathol. Commun.* **2024**, *12*, 20. [CrossRef]
144. Weskamp, K.; Tank, E.M.; Miguez, R.; McBride, J.P.; Gomez, N.B.; White, M.; Lin, Z.; Gonzalez, C.M.; Serio, A.; Sreedharan, J.; et al. Shortened TDP43 isoforms upregulated by neuronal hyperactivity drive TDP43 pathology in ALS. *J. Clin. Investig.* **2020**, *130*, 1139–1155. [CrossRef]
145. Irwin, K.E.; Jasin, P.; Braunstein, K.E.; Sinha, I.R.; Garret, M.A.; Bowden, K.D.; Chang, K.; Troncoso, J.C.; Moghekar, A.; Oh, E.S.; et al. A fluid biomarker reveals loss of TDP-43 splicing repression in presymptomatic ALS-FTD. *Nat. Med.* **2024**, *30*, 382–393. [CrossRef]
146. Calderon-Garciduenas, L.; Stommel, E.W.; Lachmann, I.; Waniek, K.; Chao, C.K.; Gonzalez-Maciel, A.; Garcia-Rojas, E.; Torres-Jardon, R.; Delgado-Chavez, R.; Mukherjee, P.S. TDP-43 CSF Concentrations Increase Exponentially with Age in Metropolitan Mexico City Young Urbanites Highly Exposed to $PM_{(2.5)}$ and Ultrafine Particles and Historically Showing Alzheimer and Parkinson's Hallmarks. Brain TDP-43 Pathology in MMC Residents Is Associated with High Cisternal CSF TDP-43 Concentrations. *Toxics* **2022**, *10*, 559. [CrossRef]
147. Calderon-Garciduenas, L.; Stommel, E.W.; Torres-Jardon, R.; Hernandez-Luna, J.; Aiello-Mora, M.; Gonzalez-Maciel, A.; Reynoso-Robles, R.; Perez-Guille, B.; Silva-Pereyra, H.G.; Tehuacanero-Cuapa, S.; et al. Alzheimer and Parkinson diseases, frontotemporal lobar degeneration and amyotrophic lateral sclerosis overlapping neuropathology start in the first two decades of life in pollution exposed urbanites and brain ultrafine particulate matter and industrial nanoparticles, including Fe, Ti, Al, V, Ni, Hg, Co, Cu, Zn, Ag, Pt, Ce, La, Pr and W are key players. Metropolitan Mexico City health crisis is in progress. *Front. Hum. Neurosci.* **2023**, *17*, 1297467. [CrossRef]

148. Yadav, A.; Verhaegen, S.; Verbruggen, E.; Kerhoas, M.; Willemijn Huiberts, E.H.; Hadera, M.G.; Berntsen, H.F.; Zimmer, K.E.; Ropstad, E.; Paulsen, R.E. A human relevant mixture of persistent organic pollutants (POPs) and perfluorooctane sulfonic acid (PFOS) differentially affect glutamate induced excitotoxic responses in chicken cerebellum granule neurons (CGNs) in vitro. *Reprod. Toxicol.* **2021**, *100*, 109–119. [CrossRef]
149. Wang, Y.; Wang, J.; Cong, J.; Zhang, H.; Gong, Z.; Sun, H.; Wang, L.; Duan, Z. Nanoplastics induce neuroexcitatory symptoms in zebrafish (*Danio rerio*) larvae through a manner contrary to Parkinsonian's way in proteomics. *Sci. Total Environ.* **2023**, *905*, 166898. [CrossRef]
150. Yu, Y.; Tan, S.; Xie, D.; Li, H.; Chen, H.; Dang, Y.; Xiang, M. Photoaged microplastics induce neurotoxicity associated with damage to serotonergic, glutamatergic, dopaminergic, and GABAergic neuronal systems in *Caenorhabditis elegans*. *Sci. Total Environ.* **2023**, *900*, 165874. [CrossRef]
151. Wu, C.; Sun, D. GABA receptors in brain development, function, and injury. *Metab. Brain Dis.* **2015**, *30*, 367–379. [CrossRef]
152. Lemon, R. The corticospinal system and ALS. *Clin. Neurophysiol.* **2024**, *160*, 56–67. [CrossRef]
153. Timmins, H.C.; Vucic, S.; Kiernan, M.C. Cortical hyperexcitability in amyotrophic lateral sclerosis: From pathogenesis to diagnosis. *Curr. Opin. Neurol.* **2023**, *36*, 353–359. [CrossRef]
154. Kiernan, M.C.; Park, S.B. Hyperexcitability, neurodegeneration, and disease progression in amyotrophic lateral sclerosis. *Muscle Nerve* **2023**, *68*, 103–105. [CrossRef]
155. Menon, P.; Kiernan, M.C.; Vucic, S. Cortical hyperexcitability precedes lower motor neuron dysfunction in ALS. *Clin. Neurophysiol.* **2015**, *126*, 803–809. [CrossRef]
156. Vucic, S.; Ziemann, U.; Eisen, A.; Hallett, M.; Kiernan, M.C. Transcranial magnetic stimulation and amyotrophic lateral sclerosis: Pathophysiological insights. *J. Neurol. Neurosurg. Psychiatry* **2013**, *84*, 1161–1170. [CrossRef]
157. Petri, S.; Krampfl, K.; Hashemi, F.; Grothe, C.; Hori, A.; Dengler, R.; Bufler, J. Distribution of GABAA receptor mRNA in the motor cortex of ALS patients. *J. Neuropathol. Exp. Neurol.* **2003**, *62*, 1041–1051. [CrossRef]
158. Gunes, Z.I.; Kan, V.W.Y.; Jiang, S.; Logunov, E.; Ye, X.Q.; Liebscher, S. Cortical Hyperexcitability in the Driver's Seat in ALS. *Clin. Transl. Neurosci.* **2022**, *6*, 5. [CrossRef]
159. Gunes, Z.I.; Kan, V.W.Y.; Ye, X.; Liebscher, S. Exciting Complexity: The Role of Motor Circuit Elements in ALS Pathophysiology. *Front. Neurosci.* **2020**, *14*, 573. [CrossRef]
160. Ding, P.; Xiang, C.; Li, X.; Chen, H.; Shi, X.; Li, X.; Huang, C.; Yu, Y.; Qi, J.; Li, A.J.; et al. Photoaged microplastics induce neurotoxicity via oxidative stress and abnormal neurotransmission in zebrafish larvae (*Danio rerio*). *Sci. Total Environ.* **2023**, *881*, 163480. [CrossRef]
161. Chatterjee, A.; Kumar, S.; Sarkar, S.R.; Halder, R.; Kumari, R.; Banerjee, S.; Sarkar, B. Dietary polyphenols represent a phytotherapeutic alternative for gut dysbiosis associated neurodegeneration: A Systematic review. *J. Nutr. Biochem.* **2024**, *129*, 109622. [CrossRef]
162. Niccolai, E.; Martinelli, I.; Quaranta, G.; Nannini, G.; Zucchi, E.; De Maio, F.; Gianferrari, G.; Bibbo, S.; Cammarota, G.; Mandrioli, J.; et al. Fecal Microbiota Transplantation in Amyotrophic Lateral Sclerosis: Clinical Protocol and Evaluation of Microbiota Immunity Axis. *Methods Mol. Biol.* **2024**, *2761*, 373–396. [CrossRef] [PubMed]
163. Lefevre-Arbogast, S.; Chaker, J.; Mercier, F.; Barouki, R.; Coumoul, X.; Miller, G.W.; David, A.; Samieri, C. Assessing the contribution of the chemical exposome to neurodegenerative disease. *Nat. Neurosci.* **2024**. [CrossRef] [PubMed]
164. Hussain, R.; Graham, U.; Elder, A.; Nedergaard, M. Air pollution, glymphatic impairment, and Alzheimer's disease. *Trends Neurosci.* **2023**, *46*, 901–911. [CrossRef] [PubMed]
165. Kiani, L. Neuronal activity drives glymphatic waste clearance. *Nat. Rev. Neurol.* **2024**, *20*, 255. [CrossRef] [PubMed]
166. Eisen, A.; Nedergaard, M.; Gray, E.; Kiernan, M.C. The glymphatic system and Amyotrophic lateral sclerosis. *Prog. Neurobiol.* **2024**, *234*, 102571. [CrossRef] [PubMed]
167. Liu, S.; Sun, X.; Ren, Q.; Chen, Y.; Dai, T.; Yang, Y.; Gong, G.; Li, W.; Zhao, Y.; Meng, X.; et al. Glymphatic dysfunction in patients with early-stage amyotrophic lateral sclerosis. *Brain* **2024**, *147*, 100–108. [CrossRef]
168. Beschorner, N.; Nedergaard, M. Glymphatic system dysfunction in neurodegenerative diseases. *Curr. Opin. Neurol.* **2024**, *37*, 182–188. [CrossRef]