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Role of the exposome in neurodegenerative disease: recent insights and future directions

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Abstract

Neurodegenerative diseases are increasing in prevalence and place significant burden on society. Causes are multifactorial and complex, and increasing evidence suggests a dynamic interplay between genes and the environment, emphasizing the importance of identifying and understanding the role of lifelong exposures, known as the exposome, on the nervous system. This review provides an overview of recent advances towards defining neurodegenerative disease exposomes, focusing on Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease. We present the current state of the field based on emerging data, elaborate on key themes and potential mechanisms, and conclude with limitations and future directions.

Graphical Abstract

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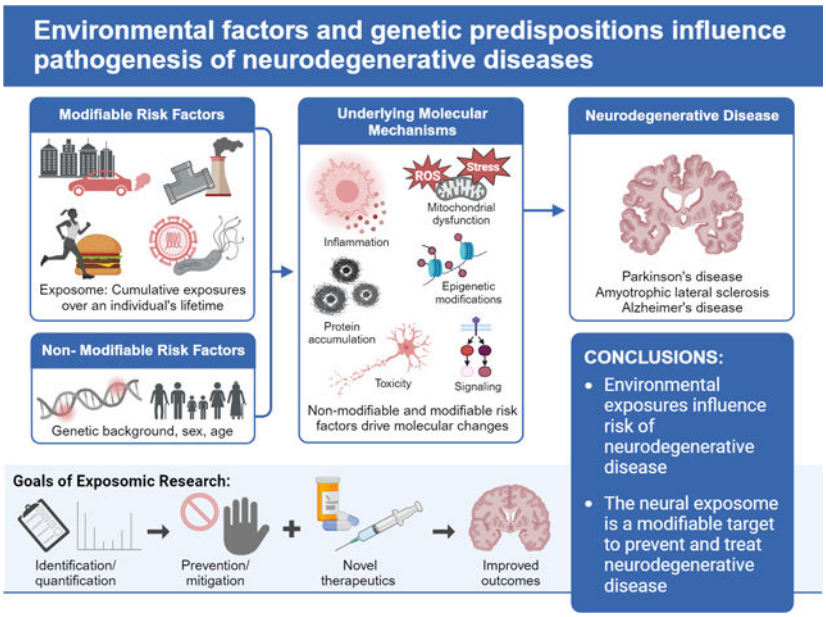

Neurodegenerative diseases are increasing in prevalence and place significant burden on society. Increasing evidence suggests a dynamic interplay between genes and the environment, emphasizing the importance of identifying and understanding the role of lifelong exposures on the nervous system. This review describes recent advances towards defining neurodegenerative disease exposomes. We present the current state of the field based on emerging data, elaborate on key themes and potential mechanisms, and conclude with limitations and future directions. Image created using BioRender.com.

Introduction

The prevalence of neurodegenerative diseases continues to increase worldwide as the global population ages. Parkinson's disease (PD) is the fastest growing neurological disorder worldwide, which doubled in prevalence between 1990 to 2015 and is forecast to double again by 2040.[1, 2] It is estimated that deaths due to motor neuron diseases, including amyotrophic lateral sclerosis (ALS), increased 12.4% from 1990 to 2019.[3, 4] Similarly, global cases of dementia topped 57 million in 2019, with an anticipated 152.8 million cases by 2050.[5, 6] This alarming rise in rates of neurodegenerative diseases places significant burdens on health systems, communities, and the economy.

Causes of neurodegenerative diseases are multifactorial and complex. Advances in genetic technology have identified mutations associated with disease.[7–9] However, for neurodegenerative diseases like PD, ALS, and Alzheimer's disease (AD), a significant proportion of sporadic and even some familial cases are of unknown genetic origins. Additionally, not all known mutations are fully penetrant and induce disease. Instead, combinations of genetic risk loci may influence an individual's susceptibility to neurodegenerative disease. Finally, heritability of neurodegenerative diseases like PD, ALS, and AD is incomplete, with single nucleotide polymorphism (SNP)-based heritability

estimates at approximately 16–36% for PD, 8–61% for ALS, and 38–66% for AD.[10–12] These estimates continue to suggest substantial influence from nongenetic factors.[7–9] Therefore, it is now widely recognized that environmental exposures, also known as the exposome, play a critical role in the development and progression of neurodegenerative diseases.[13]

The exposome, a concept first introduced by the prominent epidemiologist Chris Wild in 2005, is defined as the totality of environmental exposures throughout an individual's life, encompassing external factors such as lifestyle, diet, pollutants, chemicals, and stressors.[14] Since Dr. Wild's seminal paper in 2005, the field of exposomics has witnessed remarkable progress, evolving into a multidisciplinary approach that extends well beyond the original framing. Exposomic science now operates on an omics scale, employing high-throughput technologies to comprehensively analyze biological samples and environmental factors. This shift enables the simultaneous examination of various molecular components, including genomics, transcriptomics, proteomics, and metabolomics. By adopting these omics approaches, exposome research extends beyond traditional assessments of isolated exposures, allowing for a holistic exploration of the intricate interplay between environmental influences and biological responses.

Major large-scale projects exemplify this ambitious approach. Initiatives such as the Human Early-Life Exposome (HELIX) project and the European Human Biomonitoring Initiative (HBM4EU) aim to comprehensively and systematically characterize the exposome, employing advanced methodologies such as high-resolution mass spectrometry on biological samples. These omics approaches have played a crucial role in determining and characterizing environmental exposures associated with an increased risk of developing neurodegenerative diseases. Identifying these exposures and uncovering the intricate connections between environmental factors and the pathophysiology of neurodegenerative conditions provide opportunities to mitigate or prevent risk, enhance understanding of disease pathology, and inform treatment options. This review provides a high-level overview of the recent characterization of exposomic science in neurodegenerative disease, focusing on PD, ALS, and AD (Table 1). We present the current state of the field based on recent data within the past 5 years, elaborate on key emerging themes and potential mechanisms, and conclude with limitations and future directions.

The Neural Exposome

In the context of neurodegenerative disease, the neural exposome includes all exposures that influence nervous system health and disease.[13] These environmental exposures include pollutants, industrial and agricultural chemicals, and toxins, as well as lifestyle and social factors, diet, the microbiome, and infection (Figure 1). Acute or chronic environmental exposures may trigger neurodegenerative disease mechanisms or exacerbate existing pathological processes, either individually or in combination. These effects can be sudden and severe or delayed and gradual, accumulating and manifesting after several years.

The neural exposome is particularly complex given the dynamic and unique nature of the central nervous system (CNS).[13] The brain is selectively vulnerable to compounds that can cross the blood-brain barrier (BBB). Unlike other cells in the body, neurons can be

long-lived, rendering them highly sensitive to low-level chronic exposures. Additionally, critical windows of neurodevelopment may be more vulnerable to harmful exposures.[15]

While the penetrance of many SNPs and genetic variants in the human genome is low, their high prevalence suggest they still significantly impact disease burden. It is now appreciated that an individual's lifetime of environmental exposures dynamically interacts with their underlying genetic makeup, such as SNPs, to influence disease development and progression. This concept is known as the gene x environment (GxE) interaction.[16] Individuals may carry SNPs or genetic variants that make them more susceptible to certain neurological diseases when exposed to specific environmental factors, while others may carry variants that confer protection.[17] Environmental exposures may also influence gene expression through epigenetic modification, leading to varying outcomes in health and disease.[18] In some cases, GxE interactions create a feedback loop in which genetic factors influence an individual's environment, and the environment, in turn, influences gene expression.[18] Finally, GxE interactions that occur during critical periods of development can have long-term effects on health outcomes.[15] Identifying and understanding GxE interactions is particularly relevant in neurodegenerative disease, as these diseases typically develop later in life following a lifetime of interactions between genes and an individual's environment.[15] However, the complexity of neurodegenerative diseases like PD, ALS, and AD makes it difficult to identify single significant interactions that fully explain disease.

Investigations into the neural exposome typically consist of population and human cohort studies that use questionnaires or biosamples to identify and assess relationships between exposures and biological outcomes. Combining large genome wide association study (GWAS) datasets or genetic data with exposure information provides additional insight into the role an individual's underlying genetic susceptibility and their environment have on disease development and progression. Identification of clinically relevant exposomic risk factors is key to disease prevention and development of personalized treatment strategies.

The Neural Exposome and PD

PD is a chronic, progressive neurodegenerative disorder characterized by the progressive loss of motor control, as well as a wide range of non-motor symptoms affecting various organ systems, including cognition, mood, and autonomic functions. Loss of dopamine-producing cells in the substantia nigra leads to dopamine imbalance, which results in tremors, rigidity, bradykinesia, and postural instability.[9] PD cases are mainly sporadic (around 80%) and most risk loci identified in sporadic cases only moderately impact PD risk.[19] Instead, the majority of PD cases appear to be the result of combinations of genetic variants and environmental factors, and increasing data support the association between exposures and PD (Suppl. Table 1).

Pesticide exposure is one of the most identified PD risk factors.[20–26] Occupational exposure to pesticides is associated with advanced motor symptoms and decreased age-at-onset of PD.[23, 24] Moreover, longer duration of pesticide exposure enhances PD risk.[20, 22] Similarly, high proximity and frequent exposure to pesticides negatively correlates with age-at-onset.[24] In farmers, long-term exposure to the herbicides rotenone, diquat, and paraquat, and dithiocarbamate fungicides are particularly associated with increased PD

risk.[22] Direct measurement of organochlorine pesticide (OCP) concentrations in serum found elevated dichlorodiphenyldichloroethylene (p,p'-DDE) levels in PD patients versus healthy controls.[21] Recent studies have also investigated the GxE interactions between SNPs in genes involved in pesticide detoxification and transport and pesticide exposure. For example, butyrylcholinesterase (BChE) is a known pesticide bioscavenger and the minor allele SNP rs1803274 defines a variant of BChE with reduced serum activity.[27] Results from a recent study suggest that individuals exposed to pesticides who also carry the rs1803274 SNP within the *BCHE* gene are at increased risk for PD.[27]

Since the 1990s, numerous animal and human observational studies have examined the impact of long-term exposure to ambient air pollution, particularly airborne particulate matter ≤2.5 μM and ≤10 μM in diameter ($PM_{2.5}$ and PM_{10}, respectively), on human health, including PD [24, 25, 28–32] Several recent studies used residential addresses and land-use regression models to estimate individual exposure to air pollution based on proximity to pollution sources. These spatial analyses demonstrated significant associations between PD risk and incidence with $PM_{2.5}$, nitrogen dioxide (NO_2), and ozone (O_3) exposure.[28, 29, 33] A study examining air pollution exposure in the Negev region of Israel also identified an association between solar radiation and increased risk of PD.[33] However, the study failed to fully adjust for other factors that may expose individuals to solar radiation, such as fieldwork involving pesticides or outdoor construction that generates dust.

Metal and industrial chemical exposure may be linked to PD as well. Accumulation of metals in the nervous system can be highly toxic and cause severe neurological issues. One study in Turkey reported that most PD patients were exposed to well water compared to healthy controls, noting the possible correlation with higher metal concentrations in well water versus city network water.[30] Interestingly, Kim *et al.* noted opposing effects of elevated serum copper levels on PD risk and clinical characteristics,[31] while another study observed differences in metal speciation, such as elevated levels of manganese-albumin complexes, and not total metal concentrations, between PD and healthy controls.[32] Beyond metals, contamination of drinking water with industrial solvents, such as trichloroethylene, is also associated with increased risk of PD. Goldman et al. recently reported that the risk of PD was 70% higher in service members who resided at Marine Corps Base Camp Lejeune, whose drinking water was contaminated with trichloroethylene, tetrachloroethylene, and multiple other volatile organic compounds, than in service members who were stationed at a base with clean water.[34]

Several studies note alterations in the gut microbiome and metabolome of PD patients compared to healthy controls, and exposure to oral antibiotics, such as macrolides and lincosamides, can increase risk.[35–39] Altered bacterial composition in PD is associated with a decreased abundance of common anti-inflammatory and neuroprotective gut bacteria and increased abundance of rare gut bacteria, increasing biodiversity and potential inflammation.[35, 37] Changes in gut health also appear to play a role in PD pathogenesis, as individuals previously diagnosed with common gastrointestinal infections or intestinal disorders are at elevated risk.[40] In particular, *Helicobacter pylori* infections increases risk of PD.[41] Unfortunately, results regarding the impact of *H. pylori* eradication treatment on PD disease severity are mixed and require additional investigation.[41] Additionally, PD

patients have altered gut metabolome linked to lipid, carbohydrate, vitamin, and amino acid metabolism versus healthy controls.[37, 38]

The enigmatic relationship between smoking and PD has stirred considerable controversy within the clinical and research communities. A substantial body of evidence suggests a protective association, revealing a decreased risk of PD associated with cigarette smoking, passive smoking, and chewing tobacco.[26, 42, 43] Several meta-analyses have reported this inverse correlation, sparking interest in understanding the underlying mechanisms.[44, 45] Nicotine, the primary psychoactive component of tobacco, has been proposed as a potential neuroprotective agent, with studies suggesting its ability to prevent α-synuclein aggregation, decrease cell loss, and slow dopamine neuron degeneration, integral aspects of PD pathophysiology.[46] Additionally, studies have identified specific genetic variants that, when combined with smoking exposure, demonstrate a more pronounced protective effect against PD.[47] The interplay between these genetic factors and smoking appears to modulate key pathways related to dopamine regulation and neuronal function.[47] However, the inherent health risks associated with smoking make it a complex and paradoxical avenue of investigation.

In terms of diet, adherence to a Mediterranean diet, Mediterranean-DASH Intervention for Neurodegenerative Delay diet, and high vitamin E and C intake positively correlate with later age-of-onset and decreased risk.[48–54] Caffeine consumption and history of competitive sports is protective against cognitive decline in PD. Risk scores based on PD risks identified additive interactions between total caffeine intake and the protective effect of no family history of PD, as well as total caffeine intake and physical activity.[49] Conversely, heavy alcohol consumption is a risk factor for PD, and, interestingly, high job demand with higher education and high IQ are as well.[43, 49, 55] Regarding occupations, prolonged occupational radiation exposure or careers in counseling, social work, social services, post-secondary education, agriculture, or building and group cleaners are associated with increased PD incidence.[56, 57] The increased risk associated with occupations in counseling, social work, and post-secondary education is surprising.[58] Proposed reasons for the association include ascertainment bias due to better healthcare access, reduced risk of mortality from alternative causes such as heart disease (owing to advantageous factors like lower smoking rates), and increased exposure to infectious agents that may promote neuroinflammation.[58, 59]

The Neural Exposome and ALS

ALS is a rare, fatal neurological disease characterized by motor neuron degeneration in the brain, brain stem, and spinal cord.[7] Motor neuron death leads to progressive muscle weakness and atrophy until the ability to initiate and control voluntary movements is lost, leading to respiratory failure as the cause of death in most individuals.[7] Approximately 10–15% of ALS cases exhibit Mendelian familial inheritance patterns.[7] In these cases, heritability is higher than in sporadic cases and specific genetic mutations are often responsible.[60, 61] However, for the 85–90% of sporadic ALS cases, a known mutation is present in only 15% of patients, although a proportion of disease may be driven by rare genetic variants that are not detectable in GWAS.[62] Nevertheless, heritability in sporadic ALS is less than in familial ALS, with estimates as low as approximately 8%.[10] These

variations in heritability highlight the complex nature of ALS, with both genetic and environmental factors likely playing a role in its development (Suppl. Table 2).[63]

Air pollution is a notable contributor to disease in ALS. The recent increase in studies exploring air pollution have identified positive associations between ALS risk and exposure to $PM_{2.5}$, PM_{10}, and the gaseous pollutant NO_2, other nitrogen oxides (NO_X), sulfur dioxide (SO_2), and carbon monoxide (CO).[64–69] Air pollution also appears to aggravate ALS symptoms, as exposure to higher PM levels increases risk of ALS-related emergency department and hospital visits.[65, 69] Associations between air pollution and ALS include both residential and job-related exposures. Indeed, occupational exposure to PM, volatile organic compounds, diesel exhaust, organic dust, and polycyclic aromatic hydrocarbons have all been identified as potential ALS risk factors.[70–72]

As in PD, exposure to neurotoxic pesticides is also associated with increased ALS risk.[73, 74] Analyses of occupational histories obtained by questionnaires found that employment in the agricultural sector and occupational exposure to pesticides was higher in the ALS versus healthy control groups.[75–78] In addition, residence in areas with agricultural use is a risk factor for sporadic ALS.[79] In the United States, ALS risk positively associated with exposure to glyphosate (trade name Roundup™) and 2,4-D, two of the most commonly used herbicides.[79] Moreover, higher concentrations of polybrominated diphenyl ether (PBDE) 154, the polychlorinated biphenyls (PCBs) 118, 138, 151, and 175, and the OCP p,p'-DDE were detected in plasma of ALS participants compared to healthy controls and associated with reduced survival.[74]

Metal exposure is also considered a potential ALS risk factor. Indeed, hobbies or occupations involving metal exposure, particularly lead, are associated with increased risk of ALS and reduced survival following diagnosis.[71, 77, 78, 80–82] Studies have quantified metal concentrations in biosamples, such as deciduous teeth, toenails, and plasma, collected from ALS participants and healthy controls.[83–85] Use of deciduous teeth is particularly appealing, as they provide information regarding early life metal exposure prior to symptom onset.[83] These studies identified elevated levels of chromium, manganese, nickel, tin, and mercury in ALS participants compared to healthy controls.[83–85]

Trauma events, occupational exposure, and lifestyle factors, such as hobbies, have also been explored as potential contributors to ALS risk.[86] However, it is essential to keep in mind that research in this area is still evolving, and no definitive conclusions have been reached. Prior traumas, such as head and spinal injury, electric shock, and electrical burns, are identified as risk factors for ALS, with ALS risk increasing with the number of traumatic events.[75, 76, 80, 87–89] In recent years, a growing body of evidence has suggested a potential link between engaging in soccer and football and an elevated risk of ALS.[90–92] The rigorous physical demands and repetitive head trauma inherent in these contact sports are hypothesized to contribute to the increased vulnerability to ALS. Some studies suggest that exposure to certain environmental toxins and chemicals in specific occupational settings might be associated with increased ALS risk. For example, occupations in hunting, forestry, fishing, construction, mechanics, laundering, packaging, and military service, particularly tactical operations, and those associated with exposure to extremely low-frequency magnetic fields

are correlated with increased risk.[72, 78, 80, 89, 93–96] Smoking status has been widely studied, with cigarette pack-years and time-since-quitting positively and inversely associated with risk, respectively.[88, 97–100] Smoking is known to generate oxidative stress and inflammation, which could potentially contribute to neurodegenerative processes in ALS.

Findings regarding physical activity and alcohol consumption are inconsistent, potentially due to confounding contributions from genetic status, suggesting additional studies are needed to establish a clear link between exercise and alcohol consumption and ALS risk.[88, 97, 98] With regards to exercise, a recent study examining exercise-ALS risk interactions in a series of two-sample Mendelian randomization experiments found that acute exercise promoted expression of known ALS risk genes, such as *C9ORF72*.[101] The authors concluded that physical activity is more likely to cause motor neuron injury in individuals with ALS risk genes.[101] Additionally, a low BMI prior to symptom onset is associated with increased risk and decreased survival.[88, 97, 102] In contrast, higher-order cognitive factors, such as longer duration of education or reading 20 minutes per day, appear to be protective for ALS.[76, 98] A 2019 report reinforces this concept, having identified a negative correlation between a common genetic variation associated with higher educational attainment and ALS risk.[98] Surprisingly, type 2 diabetes or dyslipidemia have also emerged as potential protective factors.[103, 104] Despite their well-established roles as risk factors for cardiovascular diseases, studies have reported a lower incidence of ALS among individuals of European descent with a history of these metabolic conditions.[103, 104] The underlying mechanisms of these unexpected protective associations remain elusive but are postulated to be related to altered energy metabolism and homeostasis.[103]

Finally, differences in gut microbiome composition are observed between ALS participants and healthy controls.[105–110] The resulting reduction in butyrate production may promote inflammation and impair immune response in addition to damaging the digestive system.[106] Differences in gut microbiome homeostasis have also been detected, with metabolic and intracellular processing pathways downregulated in the intestinal microbes of ALS patients compared to healthy controls.[108] Additionally, increased abundance of certain microbial metabolites, such as kynurenine, are associated with increased risk of ALS.[109] A recent study suggested a possible correlation between specific gut microbiome genera and altered plasma metabolite levels, especially lipids, another noted key disease characteristic, in ALS patients.[110] Notably, the composition of the ALS gut microbiome is dynamic over the course of the disease, with a shift from protective species to neurotoxic and pro-inflammatory groups.[105] Unfortunately, probiotic supplementation in ALS patients did not bring gut microbiome compositions back to that of healthy controls or influence disease progression.[105] However, a recent case report of a female patient with ALS detailed worsening of ALS symptoms following treatment with antibiotics for a scalp injury. Use of washed microbiome transfer, an improved form of fecal microbiota transplantation by way of a transendoscopic enteral tube, successfully halted disease progression.[111] The first clinical trial evaluating the effects of fecal microbiota transplantation on disease activity and progression in ALS patients is currently underway (NCT03766321).[112] Research on the relationship between the gut microbiome and ALS is still in its early stages, and more studies are needed to establish a direct link and understand the mechanisms involved. Animal studies suggest that changes in the gut microbiome are a cause, and not a

consequence, of ALS, but this work is limited to *Sod1* and *C9orf72* mouse models.[113, 114] Therefore, additional research is required to determine whether targeting the gut microbiome could be a viable approach for ALS prevention or treatment.

The Neural Exposome and AD

AD is a progressive neurodegenerative disease characterized by cortical β-amyloid plaques, neurofibrillary tangles of tau protein, and neuronal loss, along with a gradual decline in cognitive function, which affects an individual's ability to think, reason, and remember information.[8] While dominantly inherited forms of AD were first identified in the 1930s, most cases are late-onset sporadic forms.[115] Additionally, while AD displays a high level of SNP-based heritability at around 38–66%[11] with over 40 genes/loci linked to risk,[8] twin studies support substantial influence from nongenetic risk factors[116] and several exposures associate with AD risk (Suppl. Table 3).

The 2020 *Lancet* Commission on Dementia Prevention[117] added air pollution as one of three new modifiable risk factors for dementia due to strong emerging data supporting its association with AD risk.[118–120] Recent studies corroborate these data, revealing effects of exposure to air pollution components like NO_2, $PM_{2.5}$, and PM_{10} on cortical thickness, β-amyloid deposition, and cerebrospinal fluid (CSF) levels of neurofilament light chain.[121, 122] Similarly, detrimental effects on AD neuropathological hallmarks (posttranslational histone modifications, DNA damage markers, phosphorylated tau (p-tau), and β-amyloid plaques) are seen in cohorts residing in metropolitan areas with higher exposure to combustion- and friction-derived nanoparticles.[123, 124] Notably, many of these pathologic findings were recapitulated in mice exposed to ambient air pollution.[123] A large-scale human study additionally detected an association between $PM_{2.5}$ exposure with functional measures of cognitive decline, including immediate recall and new learning.[125] Furthermore, a recent meta-analysis of studies focused on long term effects of $PM_{2.5}$ confirmed a positive association with dementia and AD diagnoses.[126]

Pesticide and metal exposures, as in ALS, have likewise gained interest for their potential association with AD risk,[127–131] but equivocal results for pesticides indicate that additional studies are needed.[132–135] For example, the Canadian Study of Health and Aging, which followed individuals over 10 years, found no significant association between PCB or OCP levels and incident dementia or AD risk; however, elevated levels of PCBs 118, 153, 156, and 163 and OCPs dichlorodiphenyltrichloroethane (DDT) and p,p'-DDE were significantly associated with lower cognitive performance scores.[135] Work in agricultural sectors also did not confer increased risk for AD in a population with dementia,[132] but a study of trichlorophenol levels in the United States revealed that individuals with higher urinary levels of the agricultural chemical 2,4,6- trichlorophenol had increased risk of AD and of all-cause mortality.[134] Metals exposure studies, on the other hand, support increased AD risk from higher aluminum, cadmium, chromium, copper, iron.[130, 136] Lead, in particular, is considered neurotoxic and aggravates pathology.[130] However, reports of associations of AD risk with arsenic are inconsistent[137–139]. A number of metals also associate with CSF p-tau and other pathologic AD biomarkers.[136] Meta-analyses support the above findings, and a

compilation of trace element data from AD participants and controls may help interrogate relevant associations as more data become available.

Like PD and ALS, lifestyle factors contribute to AD risk. Obesity, diabetes, hypertension, physical inactivity, alcohol consumption, social isolation, and smoking are among the modifiable factors noted in the 2020 *Lancet* Commission on Dementia Prevention,[117] and recent data continue to support these recommendations. Metabolic syndrome (MetS) is a cluster of interconnected rick factors, including abdominal obesity, high blood pressure, elevated fasting blood sugar levels, low HDL cholesterol, and high triglyceride levels, that increase the likelihood of developing heart disease and stroke and are also believed to affect cognitive function.[140] A recent systematic review and meta-analysis of the risk of AD in patients affected by MetS found it associated with increased risk of AD.[141] The individual components of MetS, including diabetes or obesity, also increase AD risk.[141, 142] The high risk of AD associated with diabetes and obesity lends itself to studies regarding AD risk and diet. Correlations are seen between high-fat, high-glycemic load, and other unhealthy diets to increased AD risk, while Mediterranean diet, dietary approaches to stop hypertension (DASH), Mediterranean-DASH, diets rich in flavonoids, and seafood-rich diets associate with reduced AD risk.[143–147] Both the intestinal and oral microbiome have been linked to AD risk,[148–152] and gut dysbiosis, e.g., decreased protective *Bacteroides*, decreased butyrate-producing bacteria, and increased inflammatory *Prevotella*, correlates with disease severity.[153] The neurotoxin β-methylamino-L-alanine, which was first associated with ALS and parkinsonism in Guam[154], as well as fungal and bacterial infections and certain intestinal disorders have further been linked with increased AD risk.[144, 155, 156] Finally, military service is associated with AD pathology in post-mortem brain tissue.[157]

Interestingly, interactions between lifestyle factors and known AD risk genes have been identified, particularly in apolipoprotein E 4ε (*APOE* ε4) carriers, which significantly influence an individual's response to their environment. For example, animal and human studies indicate that the *APOE* ε4 genotype increases vulnerability to adverse effects from chronic stress, poor diet, obesity, sedentary lifestyle, and metals exposure.[16] Alternatively, lifetime cognitive activity, higher educational activity, and elevated BMI later in life may be particularly protective in genetically susceptible *APOE* ε4 carriers.[16] APOE ε4 carriers also exhibited a stronger effect of air pollution on CSF neurofilament light chain levels.[122]

The Neural Exposome and Frontotemporal Dementia

Emerging research suggests environmental exposures may also influence the risk of frontotemporal dementia (FTD). FTD is a group of neurodegenerative disorders characterized by progressive degeneration of the frontal and temporal lobes of the brain, leading to changes in behavior, personality, and language. Occupational and environmental exposures, such as exposure to certain toxins or air pollution, are currently being investigated for their potential contributions to FTD risk.[158] Psychosocial factors, such as loneliness, have also been implicated, highlighting the intricate interplay between mental health and neurodegeneration.[159] Prior head trauma, diabetes, and auto-immune conditions have additionally been suggested as potential risk factors. Interestingly, a study published in 2022 reported that patients with FTD had lower prevalence of hypertension and

hypercholesterolemia than health controls.[160] Clearly, the role of environmental exposures in FTD pathology is an evolving field and more studies are needed to elucidate the specific environmental factors and their interactions with genetic predispositions that contribute to FTD.

Key Emerging Themes

As evident above, several shared exposures emerge across studies of different neurodegenerative disease exposomes, including certain air pollution components, pesticides, and metals (Table 1). These similarities suggest that common mechanisms underlying CNS damage may be at play, and thereby offer insight into pathways and targets that could inform potential therapeutic development. Below, we discuss a few of the key emerging themes in neural exposome studies associated with PD, ALS, and AD, including what is known about how these factors contribute to neurodegeneration.

Mechanisms by which air pollution influences risk of neurodegenerative disease—Exposure to air pollution may increase risk of neurodegenerative disease by directly damaging CNS structures or predisposing the brain to neurodegenerative disease (Figure 2). There is an urgent need to understand the biological mechanisms underlying air pollution exposure, as exposure at any point during an individual's life, even as early as childhood, can have lasting influence on neurodegenerative pathogenesis.[63, 161]

Air pollution is composed of PM and gaseous pollutants that can reach the brain through the blood stream or via inhalation through the olfactory system.[162] Air pollution components can directly trigger neuronal toxicity and induce CNS inflammation by weakening the BBB, allowing access of additional toxicants to the brain, where they bioaccumulate and activate microglia.[162] In tandem, airway exposure to air pollution can induce a systemic inflammatory response, which subsequently impacts the CNS and promotes neurodegeneration.[162] The respiratory epithelial lining acts as a barrier to protect the body from air pollution,[162] but produce proinflammatory cytokines that trigger immune cell activation following exposure to air pollution.[162] Systemic inflammation disrupts BBB integrity, which enables pro-inflammatory cytokines and immune cells to enter the CNS and induce neural inflammation and injury.[162] Sustained neural inflammation may intensify signaling of pathways involved in aging and promote progressive neuronal damage.[163]

In vitro studies suggest that another adverse effect of air pollution is induction of oxidative stress.[163] In AD, increases in CNS oxidative damage associate with neurodegeneration and disease pathogenesis.[163] Air pollution may also promote AD by accelerating neuronal accumulation of β-amyloid peptides and p-tau, key AD features.[163] Of interest to PD, exposure to diesel exhaust particles causes α-synuclein accumulation in mouse and zebrafish brains, a classic PD pathology.[162]

Finally, emerging topics of interest implicate indirect neurotoxic mechanisms of air pollutants.[119, 162, 164] For one, air pollutants may induce alterations in microbiome diversity, which are then linked to downstream neurodegenerative mechanisms as described above. Additionally, air pollution may activate the sympathetic adrenal-medullary and hypothalamus-pituitary-adrenal axis stress responses, which are associated with deleterious

brain structural changes.[119, 162, 164] However, these are relatively new areas of research and further studies are needed to validate animal *in vivo* findings in the human adult brain.

Mechanisms by which OCPs influence risk of neurodegenerative disease— OCPs are a class of stable synthetic chemicals that were widely used as pesticides, are extremely persistent in the environment, and bio-accumulate in lipid-rich tissues. Examples of OCPs include p,p'-DDE, DDT, dieldrin, and endosulfan. Though many OCPs have been banned or restricted in the United States due to their potential health risks, they can still be found in the environment and may continue to pose a threat to human health. Additionally, individuals may come in intact with OCPs through food from regions where they are not banned and are still commercially used for pesticide control.

The mechanisms through which chronic exposure to OCPs contribute to the development of neurodegenerative disease are not yet fully understood but are thought to be related to their neurotoxic properties (Figure 3).[63] OCPs can cross the BBB and, as they are lipophilic compounds, accumulate in lipid-rich brain tissue where they directly affect neuronal function and survival. Several cell and animal studies demonstrate the ability of OCPs to induce apoptotic cell death and neural degeneration through mitochondrial dysfunction, reactive oxygen species (ROS) production, and oxidative stress,[165] which promote microglial activation and subsequent neuroinflammation. Indeed, oxidative damage is observed in the nigrostriatal region of animals models exposed to chronic low-doses of dieldrin.[165] In rats, endosulfan exposure reduces levels of catalase, glutathione, and superoxide dismutase.[165] OCPs are also linked to lipid oxidation in mitochondrial membranes, which can further impair mitochondrial function.[166] Mitochondrial dysfunction and neuroinflammation are increasingly recognized as significant contributing factors in the pathogenesis of various neurodegenerative diseases.[167, 168]

Exposure to environmental toxins, including OCPs, is also linked to epigenetic changes and altered gene expression patterns.[165] In cell and mouse models, dieldrin exposure induces hyperacetylation of core histones H3 and H4 and epigenetic dysregulation.[165] *In utero*, exposure to dieldrin leads to fetal genome-wide DNA methylation, including genes involved in dopaminergic neuron development and PD.[169]

Relevant to AD*, in vitro* studies suggest that certain OCPs might promote the production and aggregation of β-amyloid and influence tau abnormalities in the brain, potentially contributing to disease pathology.[165, 170] In PD, it is thought that OCPs may interfere with dopamine pathways in the brain by disrupting dopamine synthesis, inhibiting dopamine reuptake, and modulating dopamine receptors. In mice, exposure to dieldrin decreases levels of the dopamine metabolites 3,4-dihydroxyphenylacetic acid and homovanillic acid and disrupts expression of the PD-associated proteins dopamine transporter and vesicular monoamine transporter 2, while increasing expression of α-synuclein as well as glial fibrillary acidic protein, a marker of astrocytic activation.[171] Similarly, endosulfan exposure depletes dopamine levels.[165] Finally, dopaminergic neurons appear to be more sensitive than other cell types to OCP-induced neurotoxicity.[165]

Overall, evidence linking OCP exposure to neurodegenerative disease is limited and sometimes conflicting. More research is needed to establish a definitive causal relationship, identify specific organochlorines that might be involved, and understand the underlying mechanisms.

Mechanisms by which metals influence risk of neurodegenerative disease— Environmental metal exposure includes exposure to both essential metals (iron, copper, zinc, and manganese) and toxic metals (lead, aluminum, and cadmium), which can impact neuronal health via many mechanisms (Figure 4).[130] Chronic exposure to toxic metals through environmental sources, such as contaminated water, air, or occupational exposures, may damage the BBB.[172] The BBB normally restricts the entry of many substances, including toxic metals, into the brain. Disruption of the BBB may allow increased passage of toxic metals into the brain and contribute to the accumulation of these metals over time. Under homeostatic condition, essential metals serve as cofactors for biological molecules and enzymes and are thus involved in many cellular processes. Alterations in essential metal homeostasis and accumulation of toxic metals promotes oxidative stress, protein accumulation, and neuroinflammation, all of which may contribute to neurodegenerative disease pathogenesis.[130]

Oxidative stress is a known contributing factor to neurodegenerative disease progression.[173] Given that some essential metals play important roles in redox reactions, essential metal overexposure can promote generation of ROS.[130] Excess ROS disrupts mitochondrial function and induces an oxidative stress response. Like essential metals, toxic metals can also promote ROS generation. However, toxic metal accumulation also impairs antioxidant responses by inactivating the antioxidant glutathione and decreasing activity of the antioxidant enzymes catalase, glutathione peroxidase, and superoxide dismutase 1, the latter of which is mutated in approximately 10% of familial ALS cases.[130] Additionally, excess aluminum can liberate iron from iron-containing enzymes and proteins. This increases free iron concentrations, which subsequently promotes additional ROS production.[130]

Metals may also induce protein misfolding and accumulation, a key pathologic hallmark across neurodegenerative diseases.[8, 9] Essential metal overload promotes β-amyloid, p-tau, and α-synuclein aggregation through direct binding and ROS production.[130, 174] Both essential and toxic metals also induce β-amyloid accumulation and plaque formation through increased expression of amyloid precursor protein and beta-secretase 1, disrupting plaque clearance.[130] Similarly, metal overexposure promotes tau hyperphosphorylation and accumulation by upregulating tau mRNA, enhancing activity of tau kinases, and inhibiting activity of tau phosphatases.[130]

Finally, like air pollution, essential metal dyshomeostasis and chronic toxic metal exposure, induces pro-inflammatory responses that promote neuroinflammation and subsequent neuronal toxicity.[173] Metals, such as iron, copper, and lead, activate microglia and promote overproduction and release of the pro-inflammatory proteins and cytokines nitric oxide synthase, TNF-α, IL-1B, IL-6, and IL-8,[130] which are known to contribute to neurotoxicity in neurodegenerative disease.[130]

Overall, several shared mechanisms underlie environmental exposures that elevate the risk of neurodegenerative diseases, with oxidative stress and inflammation emerging as pivotal contributors. These pathways promote neurodegenerative diseases by triggering cascades of cellular damage, impairing crucial protective mechanisms, and contributing to the progressive degeneration of neural tissue. Thus, there is a critical need to understand and mitigate oxidative stress and inflammation for effective preventative strategies.

Current Limitations and Future Perspectives

Limitations—While exposomic studies have provided extensive information regarding the role of environmental risk factors in neurodegenerative disease, multiple challenges and questions remain. First, the neural exposome is difficult to study due to its complex and dynamic nature. The duration, frequency, and number of exposures can all vary in a single individual. In neurodegenerative diseases that develop later in life, exposures may occur decades before onset of symptoms. Additionally, tools and strategies are needed to model combinations of exposures.[13] Second, available sensitive quantification methods using biological samples or legacy biomarkers for specific exposures are time-consuming and costly.[175] Most exposomic studies rely on questionnaires to assess exposure, which are subject to recall bias and some individuals may not even be aware they were exposed. Third, given the large number of compounds in the environment, exploratory studies are needed to detect novel environmental risk factors. Unbiased metabolomic profiling may be useful in detecting the presence of novel compounds, but the identities of specific compounds are difficult to determine without appropriate libraries of standards.[175]

Additionally, the majority of studies exploring the impact of the neural exposome on PD, ALS, and AD rely on case-control or cohort study designs. While these methodologies have provided valuable insights, it is crucial to acknowledge their inherent limitations, notably the risk of establishing mere associations rather than causative relationships. Recognizing this challenge, several Mendelian randomization studies have been performed to investigate causal relationships. For example, a study by Domenighetti *et al.* investigated the association between lifestyle behaviors (smoking, alcohol, and coffee consumption) and PD using two-sample Mendelian randomization.[176] Results indicated a significant inverse association between smoking initiation and PD, and this association was not explained by reverse causation, confounding, or biases. A two-sample Mendelian randomization study to assess potential causal connections between gut microbiota, metabolites, and neurodegenerative diseases detected suggestive associations between specific gut microbiota and metabolites and PD, ALS, and AD.[109] However, it is imperative for clinicians and researchers to approach these findings with caution, as Mendelian randomization studies are not immune to pitfalls, such as pleiotropy, potential biases in the selection of instruments, and small sample sizes, underscoring the need for a comprehensive and multidimensional approach to unraveling the intricate web of environmental influences on neurodegenerative diseases.

Finally, studying the neural exposome is challenging due to the intricate interplay between environmental exposures, individual genetic susceptibility, underlying health conditions, and lifestyle factors, resulting in varied and unpredictable responses of different individuals to the same neurotoxic substances. For instance, as described in detail above, air pollution

is a significant risk factor for PD, ALS, and AD. This heterogeneity underscores the complex nature of neurodegenerative diseases and emphasizes the need for a comprehensive understanding of both genetic predispositions and environmental influences in unraveling the intricacies of the neural exposome.

Future perspectives—It is estimated that in the next 10 years, over 100,000 registered compounds will be present in the United States environment.[15] Epidemiological studies alone are insufficient to analyze the potential risk and neurotoxicity from these compounds. Instead, cell- and model organism-based screening approaches in controlled lab settings will be necessary to narrow down compounds of interest and accelerate discovery.[15] Additionally, recent advances in high-resolution mass spectrometry allow comprehensive characterization of environmental chemicals and endogenous metabolites in biological samples. Use of large screening libraries will enable identification of previously unknown exposures, analyzing environmental chemical-metabolomic associations, which will provide important insight into the interactions between exposures and hosts.[177] Continued characterization of GxE interactions is likewise critically important to decipher underlying disease mechanisms, prevent exposure, and develop personalized therapies.

As detailed above, historical/retrospective exposomics studies have many limitations. However, prospective studies provide a promising alternative. Large-scale, multi-national collaborative studies that follow cohorts of individuals prior to disease onset and collect multiple sample types, both biological and environmental, throughout the study will provide robust data and methods for investigators to trace disease to previous exposures.[177] Data from service agencies or industries should also be incorporated into existing datasets to improve quantification of environmental hazards and exposures.[144] Geospatial analyses can similarly locate clusters of disease cases and determine if clusters are located around possible exposure sites, such as urban areas, high-risk industrial zones, heavy traffic, or farmland.

Additionally, mechanistic research is desperately needed to determine biological relevance of the multitude of identified compounds and their potential effect on the nervous system, which will guide development of treatment and prevention strategies. With that goal in mind, the National Institute of Neurological Disorders and Stroke recently opened the new Office of Neural Exposome and Toxicology (ONETOX) to foster multi-disciplinary, collaborative basic, translational, and clinical research on the exposome in neurological disease.[13]

Of interest, initial reports suggest a decline in incidence of dementia,[178] which carries significant implications when viewed through the lens of the neural exposome. This trend suggests that improvements in public health interventions and medical care over time, such as better management of cardiovascular risk factors and increased awareness of the importance of a healthy lifestyle, and guidelines focused on modifiable risk factors to support prevention[117], due to increased understanding of the neural exposome may be having a positive impact.[179] These promising results extend beyond dementia, indicating that efforts to address modifiable risk factors within the neural exposome can potentially influence the trajectory of other neurodegenerative diseases like ALS, PD, and AD.

With all of this in mind, urgent measures are therefore needed to regulate these harmful environmental factors that contribute to conditions like PD, ALS, and AD. Robust public health initiatives should be established to raise awareness regarding the potential risks associated with specific environmental exposures and promote lifestyle changes that minimize these risks. Simultaneously, collaborative efforts between the scientific community, policymakers, and industry stakeholders are essential to develop and implement stringent regulations that curb the release of harmful substances into our environment. As companies in the past have concealed potential health risks, such as those associated with paraquat[180], it is also critical to remain vigilant in scrutinizing industries for transparency in reporting potential risks associated with their products. These steps must be taken sooner rather than later, as the seeds of future generations of individuals with neurodegenerative diseases may already be planted. By fostering a comprehensive, multidisciplinary approach, we can strive to create a healthier environment and mitigate the risk factors contributing to the alarming rise of neurodegenerative diseases in our communities.

Concluding Remarks

The neural exposome provides a modifiable target to curb the alarming global rise of neurodegenerative diseases. There is now a critical need for large-scale, multi-national, and multi-disciplinary studies to identify and determine the biological relevance of exposures and the potential mechanisms by which they impact neurodegenerative disease pathogenesis. Ultimately, identifying the factors that alter risk and determining their role in disease pathogenesis will inform neurodegenerative disease prevention strategies and guide the development of novel treatment options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary for Social Media if Published

1. Twitter handle(s) to tag: @EvaFeldmanMDPhD

2. What is the current knowledge on the topic?

The exposome – the full spectrum of environmental exposures that shape a person's life - is an emerging area of research in the context of neurodegenerative disease. From pollutants to lifestyle choices, there is growing evidence that these factors may play a critical role in conditions like Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease. However, researchers are still unraveling the story of how our surroundings could be key players in these devastating diseases.

3. What question did this study address?

This review provides a closer look at the specific environmental factors that shape and advance neurodegenerative diseases.

4. What does this study add to our knowledge?

This review sheds new light on the complex interplay between environmental exposures and neurodegeneration. It breaks down important themes and potential mechanisms, while also addressing current challenges in the field. By doing so, it aims to guide future research and potential interventions.

5. How might this potentially impact on the practice of neurology?

A comprehensive understanding of how the exposome affects neurodegenerative diseases could help physicians tailor care to each patient and prevent problems before they arise. Pinpointing and dialing down specific environmental risks may lower the chances and seriousness of neurodegenerative conditions. And that's a win for everyone – better outcomes and a better life for patients.

Draft Tweet: Neurodegenerative diseases are on the rise. It's time to unravel the neural exposome to combat disease and shape a healthier future.

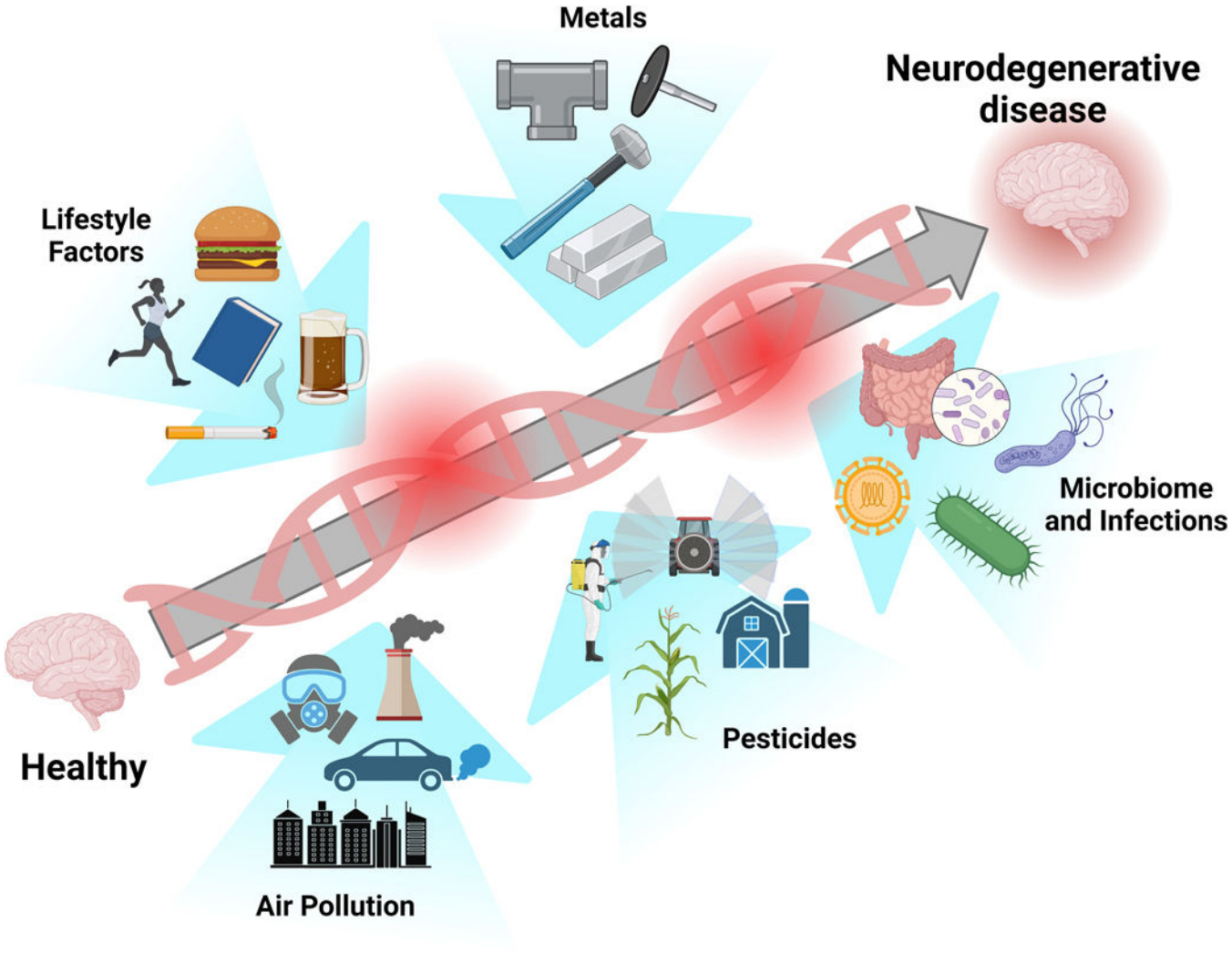

Figure 1. The neural exposome.

The cumulative external and internal factors individuals are exposed to over the course of their lifetime. Exposures may interact with underlying genetic background (risk-modifying single-nucleotide polymorphisms represented by red shaded circles) to influence risk of neurodegenerative disease. Image created using BioRender.com.

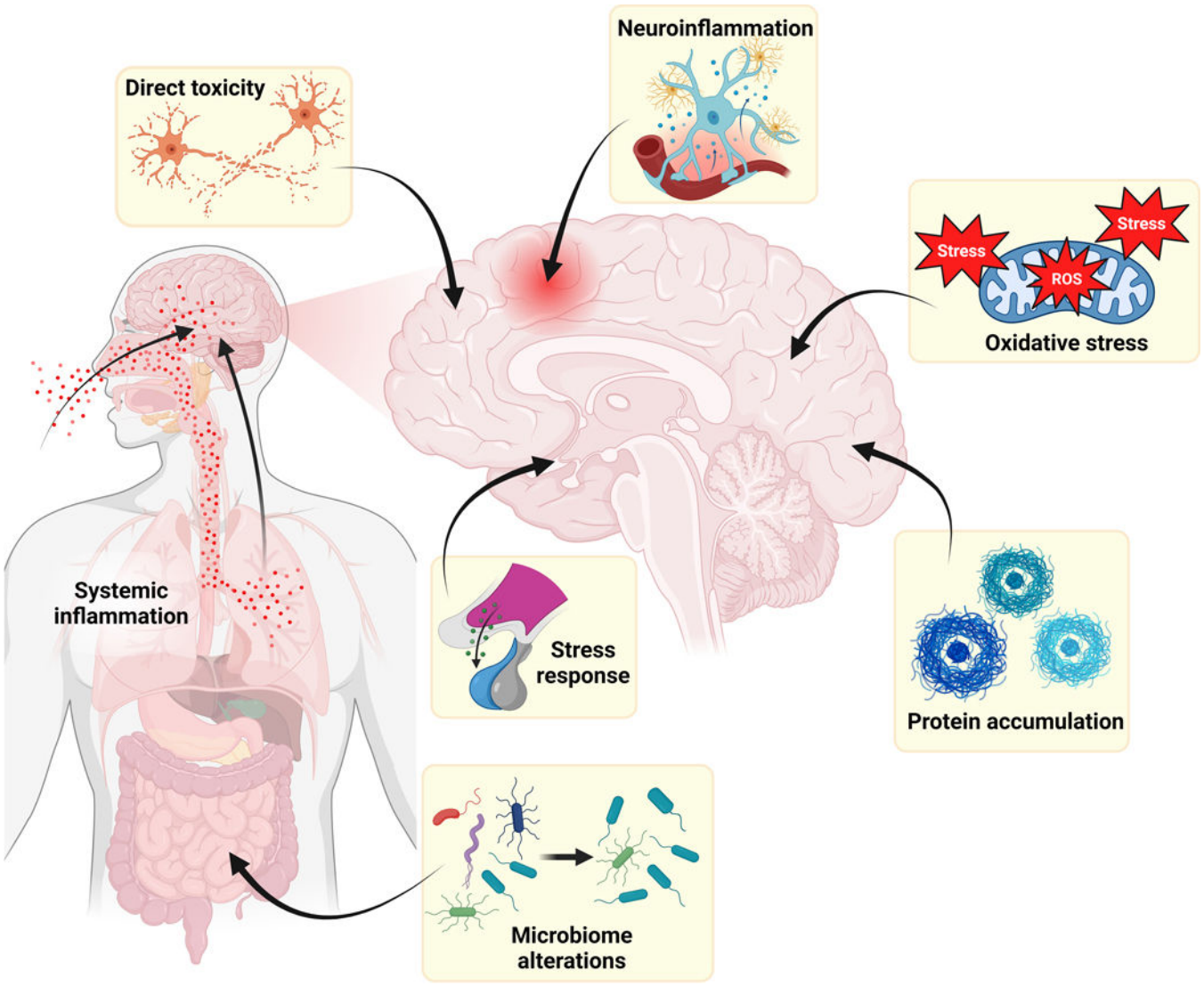

Figure 2. Potential mechanisms by which air pollution influences risk of neurodegenerative disease.

Inhaled air pollution components access the brain directly through the olfactory system or indirectly through the blood stream and cause neurotoxicity and neuroinflammation. Airway epithelial cells trigger a systemic inflammatory response, which compromises the BBB. In the brain, components of air pollution induce oxidative stress, accumulation of proteins, e.g., β-amyloid and phosphorylated tau, and activates the hypothalamus-pituitary-adrenal axis. In the gut, air pollution changes the gut microbiome. Image created using BioRender.com.

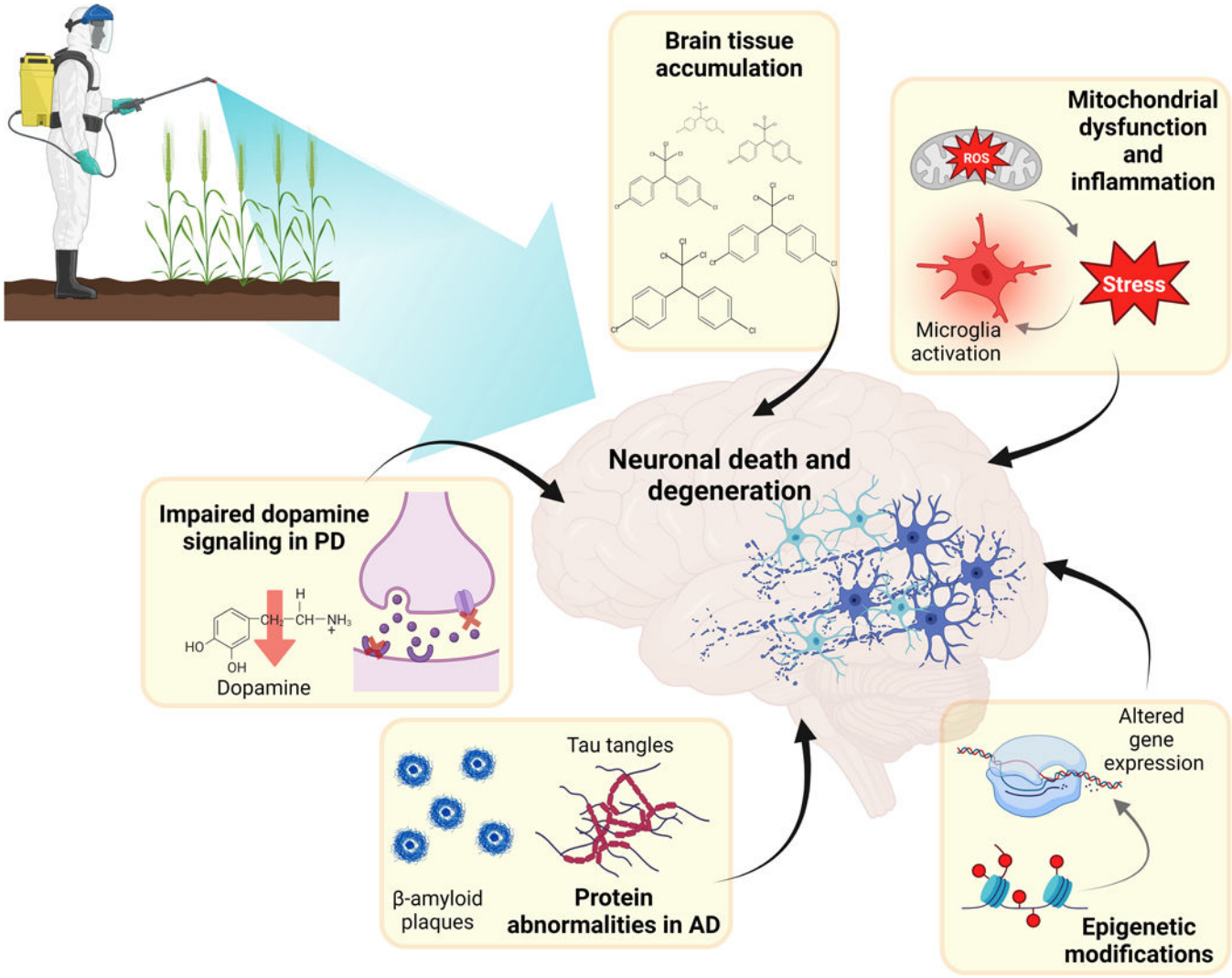

Figure 3. Potential mechanisms by which OCPs influence risk of neurodegenerative disease.

OCPs cross the BBB and accumulate in lipid-rich brain tissue where they can affect neuronal function and survival through mitochondrial dysfunction, reactive oxygen species (ROS) production, oxidative stress, and microglial activation. OCP-induced histone hyperacetylation and genome-wide DNA methylation can also induce epigenetic dysregulation of gene expression. In AD, OCPs promote aggregation of β-amyloid and phosphorylated tau. In PD, OCPs disrupt dopamine synthesis, inhibit dopamine reuptake, and impact dopamine receptors and transporters. Image created using BioRender.com.

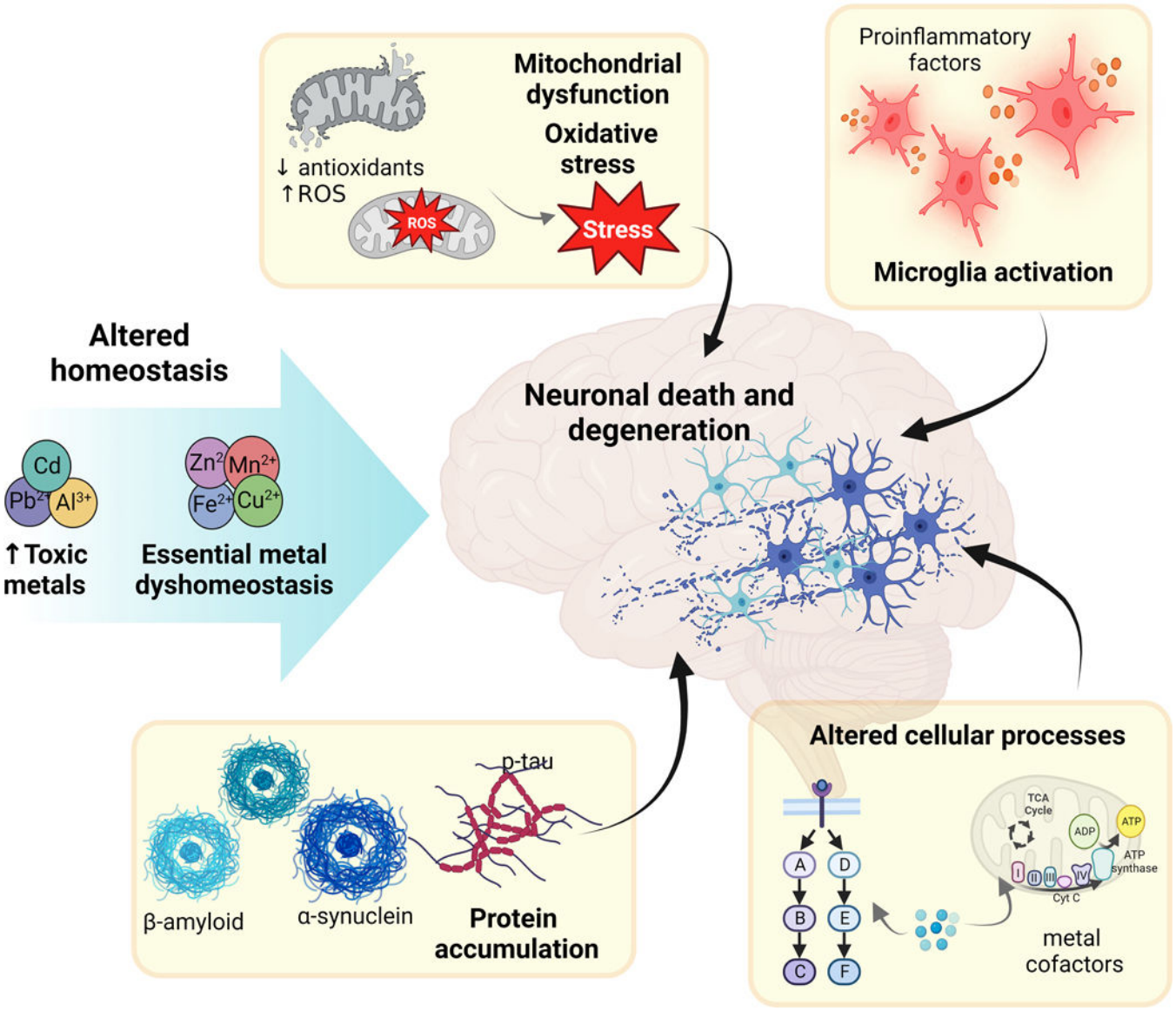

Figure 4. Potential mechanisms by which metal overexposure influences risk of neurodegenerative disease.

Essential metal dyshomeostasis or toxic metal accumulation induces reactive oxygen species (ROS) generation, which increases oxidative stress and impairs mitochondrial function. Dyshomeostasis of essential metals disrupts cellular processes. In addition, metal binding or metal-induced alterations in protein expression and activity facilitates accumulation of β-amyloid, phosphorylated tau, and α-synuclein. Metal overload promotes neural inflammation through microglial activation and production of proinflammatory cytokines. Image created using BioRender.com.

Table 1.

Summary and comparison of PD, ALS, and AD exposomes[a]

	PD	ALS	AD
Global prevalence (n/100,000)	106	5	682
Average age at diagnosis (yrs)	60	55	85
Heritability (%)	16–36	8–61	38–66
Familial (%)	10–15	10–15	1–5
Prominent genetic factors of interest	*SNCA*	*C9ORF72*	*APP*
	LRRK2	*TARDBP*	*PSEN1*
	PRKN	*SOD1*	*PSEN2*
	GBA	*FUS*	*APOE*
Exposures increasing risk[b]			
Air pollution	$PM_{2.5}$, NO_2, O_3	$PM_{2.5}$, PM_{10}, NO_2, NO_X, SO_2, and CO	$PM_{2.5}$, PM_{10}, NO_2
Pesticides	p,p'-DDE	P,p'-DDE, α-hexachlorocyclohexane, hexachlorobenzene, PCBs	2,4-DDE, γ-hexachlorocyclohexane/ PCBs
Herbicides/fungicides	Rotenone, diquat, paraquat, dithiocarbamate	2,4-D, glycophosate	2,4,6-TCE
Metals	Cu, Fe, Zn	Cd, Mn, Sn, Pb	As, Cr, low Se
Occupation	Agriculture/forestry/ fishing, textile manufacturing, metal manufacturing	Production, military, agriculture	Military
Smoking		Smoking	Smoking
Trauma		Head injury, electric shock	
Lifestyle	High IQ, alcohol usage	Competitive sports, alcohol usage	Obesity, diabetes, alcohol usage
Microbiome	Decrease in butyrate-producing bacteria, *H. pylori* infection	Decrease in butyrate-producing bacteria	Decrease in butyrate-producing bacteria
Gene x environment example	Rs1803274 SNP variant of the pesticide bioscavenger *BCHE* increases risk	Acute exercise promotes *C9ORF72* expression	APOE ε4 genotype increases risk associated with stress, poor diet, obesity, sedentary lifestyle, and metals exposure

2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DDE, 2,4-dichlorodiphenyldichloroethylene; 2,4,6-TCE, 2,4,6-trichloroethylene; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; IQ, intelligence quotient; PCBs, polychlorinated biphenyls; PD, Parkinson's disease; p,p'-DDE, p,p'-dichlorodiphenyldichloroethylene ;SNP, single nucleotide polymorphism.

[a]Data noted in the table are drawn from references cited in the text.

[b]Listed exposures described in the current review are taken from studies published between 2018–2023 and that are associated with increased risk. See Supplemental Tables 1–3 for additional details.