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Air Pollution–Related Neurotoxicity Across the Life Span

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Abstract

Air pollution is a complex mixture of gases and particulate matter, with adsorbed organic and inorganic contaminants, to which exposure is life-long. Epidemiological studies increasingly associate air pollution with multiple neurodevelopmental disorders and neurodegenerative diseases, findings supported by experimental animal models. This breadth of neurotoxicity across these central nervous system diseases and disorders likely reflects shared vulnerability of their inflammatory and oxidative stress–based mechanisms and a corresponding ability to produce brain metal dyshomeostasis. Future research to define the responsible contaminants of air pollution underlying this neurotoxicity is critical to understanding mechanisms of these diseases and disorders and protecting public health.

Keywords

air pollution; ultrafine particles; $PM_{2.5}$; neurodevelopmental disorders; neurodegenerative disease; brain metal dyshomeostasis

1. ELUSIVE ETIOLOGIES OF NEURODEVELOPMENTAL DISORDERS AND NEURODEGENERATIVE DISEASES: DOES AIR POLLUTION PLAY A ROLE?

Extensive efforts have been undertaken to delineate the underlying etiologies of neurodevelopmental disorders (NDDs) such as autism spectrum disorder (ASD), schizophrenia (SCZ), and attention deficit hyperactivity disorder (ADHD) and neurodegenerative diseases (NDGDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS). Both NDDs and NDGDs are increasing in prevalence. Efforts to link these NDDs and NDGDs to genetic etiologies alone have proven to be of limited explanatory capacity, especially when considered in relation to increasing prevalence.

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Albeit still at a relatively early stage, a sizeable body of epidemiological research has now associated these NDDs and NDGDs with exposures to air pollution (AP). To date, the development of animal model–based research has been more limited, particularly for studies based on human-relevant exposure conditions, likely because of the paucity of facilities for ambient whole-body inhalation exposures. Nevertheless, considered collectively, the epidemiological and animal model studies already provide strong support for a role of AP exposures in both NDDs and NDGDs and as such have marked significance for clinical and public health. The findings also support revised consideration of environmental regulations for such exposures.

This review highlights the epidemiological evidence from meta-analyses examining associations of AP with NDDs and NDGDs as well as evidence of human brain pathology. Importantly, animal model results are noted, summarized, and reviewed. This is followed by a discussion relating the breadth of central nervous system diseases and disorders associated with AP to the shared features of NDDs and NDGDs and to brain metal dyshomeostasis, and of why such disorders could increase even as air quality improves. Lastly, some specific considerations for future research are presented.

2. AIR POLLUTION: A COMPLEX MIXTURE OF PARTICLES AND GASES AND ADSORBED CONTAMINANTS

AP is actually a complex mixture that includes primary pollutants emitted directly from a source and secondary pollutants consequently formed in the atmosphere from chemical reactions. Specifically, AP is largely a product of vehicle exhaust and industrial emissions, and it includes particles with adhering volatile organic and inorganic contaminants [including metals and trace elements (1)], which are adsorbed onto a carbon base, and atmospheric gases (CO_2, CO, NO, ozone, SO_2). As such, environmental ambient AP is a dynamic complex mixture, the components and chemistry of which continuously change over time (even very brief time periods) in response to conditions that include weather, season, geography, and local industry and traffic conditions, among others (2). To focus the scope of this review, discussion is restricted primarily to particulate matter (PM) toxicity.

AP health effects are related to PM size, traditionally designated as coarse (<10 μm, or PM_{10}), fine (<2.5 μm, or $PM_{2.5}$), or ultrafine particles (UFPs) (<100 nm or 0.1 μm; nanoparticles). With a greater surface area per mass ratio for contamination by organic and inorganic contaminants, UFPs are considered the most reactive component of AP (3). Specific contaminants of UFPs are highly dependent upon chemical interactions with airborne gases, as well as with geographical area and associated industries and traffic conditions. Current regulation of PM AP exposures in the United States, which is overseen by the Environmental Protection Agency, is restricted to levels of PM_{10} and $PM_{2.5}$, while UFPs, despite their greater potential for contamination, are not currently regulated, based on both the contention that their toxicity is insufficiently established and the current lack of adequate monitoring data. Gases in AP, specifically CO, SO_2, and NO_2, are also regulated in the United States, as is one other contaminant, the metal lead (Pb). The current annual

primary standard for $PM_{2.5}$ in the United States is 12 μg/m^3, while the updated annual average World Health Organization guidelines are 5 μg/m^3.

As this complexity indicates, outcomes across human studies of AP can be difficult to compare, even for comparisons based on, for example, only exposures to $PM_{2.5}$, the adsorbed contaminant profiles can differ, meaning that the populations were exposed to a different chemical mixture. An understanding of AP health effects will require speciation of the chemical composition of the exposures to determine which contaminant(s) underlies observed neurotoxicity. Such information could be used to implement new regulations for controlling these contaminants in AP.

3. ROUTES OF AIR POLLUTION TO THE BRAIN: A LIFELONG EXPOSURE

The potential toxicity of AP to the brain is augmented by its multiple routes of exposure across life. In utero, AP PM inhaled by the mother can directly affect placenta and thereby influence fetal brain development (4). Animal models further support such a mechanism. For example, nose-only diesel exhaust exposure inhalation reduced placental efficiency and decreased placental blood flow and fetal vessel volume (5), while concentrated inhaled $PM_{2.5}$ exposure for 15 days of gestation in rats reduced placental mass, size, and surface area (6), suggesting that a placental inflammatory reaction had taken place (7). A recent study of occupational exposures to nanoparticles based on a job exposure matrix found UFP exposures to be associated with placental hypoplasia (8). A review of human perfused placenta noted that placental transport was dependent on characteristics that included size and surface modifications of PM (9).

Adsorbed contaminants may also cross the placenta. Trace elements essential to fetal brain development can cross from maternal into fetal circulation. Both iron (Fe) and sulfur (S), for example, move actively into fetal circulation. The fetal need for Fe actually increases across pregnancy (10), with Fe traversing fetal endothelium to reach fetal circulation (11). Other nanoparticle-based metal contaminants shown to be capable of placental transfer and accumulation in fetal tissue include Pb, cadmium, mercury, copper (Cu), and vanadium (12, 13). In the case of Fe, regulatory mechanisms for its homeostasis within the brain are not established until later in development (14), thus leaving the fetal brain potentially vulnerable to early trace metal accumulation and consequent brain metal dyshomeostasis.

Following birth, both direct and indirect exposure routes to the brain are operative. While differences in deposition within lung regions occur in response to particle size, UFPs show efficient translocation into the blood circulation (15), from which they can then travel into the brain.

Of additional concern are extrapulmonary routes of exposure, consisting of nasal olfactory uptake and brain distribution via olfactory and trigeminal nerves (16). These nanoparticles/contaminants actually bypass the blood-brain barrier and thus are not necessarily indexed by peripheral markers (17). A study comparing levels of metals in postmortem brain tissue and ventricular fluid in individuals with AD and nondemented elderly controls reported that brain metal concentrations were elevated in individuals with AD, whereas levels in

ventricular fluid were not indicative of brain metal concentrations in either group (18), with the exception of Pb. Metals and trace elements shown to be taken up into the brain via this pathway to date (19) include manganese (Mn), cadmium, Pb, Fe, uranium, nickel, thallium, cobalt, chromium, zinc (Zn), mercury, and aluminum (Al). Notably, increases in and imbalance of such metals, particularly Fe, have been implicated in multiple NGDGs, including AD and PD (20). Furthermore, brain trace metal imbalances have been implicated in multiple other NDGDs as well (21). Whether translocation occurs via the vagal nerve to the brainstem has yet to be ascertained.

The lack of clear mechanisms for removal of metal contaminants from the brain further exacerbates concern regarding the nasal olfactory route. Fe was reported to have an extremely slow turnover in rodent brain (half-life of approximately 9 months), with estimates on the order of decades when extrapolated to humans (22). Further, a recent study reported that Fe deposition in the brain may lead to dysfunction of the glymphatic system, which is considered an important fluid clearance system of the brain (23).

4. EPIDEMIOLOGICAL EVIDENCE FOR A ROLE OF AIR POLLUTION IN NEURODEVELOPMENTAL DISORDERS AND NEURODEGENERATIVE DISEASES

Given the scope of the epidemiological literature, the review of population exposure effects here focuses primarily on the most recent meta-analyses of studies that have utilized $PM_{2.5}$ as the relevant exposure. These studies have primarily focused on exposures during pregnancy and/or early development, or on aging populations. Human studies without specific exposure metrics were not included.

4.1. Epidemiological Studies and Meta-Analyses of Neurodevelopmental Disorders

Epidemiological studies of the role of AP in NDDs have been reported in populations from multiple different countries based on different metrics of exposure, such as PM levels or surrogates of traffic such as NO_x parameters. As noted above, given the breadth of sites from which such studies emerge, the specific contaminants and their levels within AP will also necessarily differ. Nevertheless, a substantive body of positive associations have emerged as indicated in recent meta-analyses.

Studies of ASD, the most extensively examined NDD in relation to AP exposures, have reported both positive and null associations across studies. However, recent meta-analyses suggest a positive overall significant link (24–26). The most recent meta-analysis (which included 28 studies that corresponded to a total of 758,997 newborns, of which 47,190 were diagnosed with ASD) found that increases of 5 $\mu g/m^3$ of $PM_{2.5}$ increased risk of ASD regardless of the model used, whether AP exposures were examined during preconception (+17% risk), pregnancy (+5–16%, dependent upon model), or the postnatal period (+11–16%), suggesting a broad period of vulnerability, although the most consistent effects were found with exposures during pregnancy (26). These findings were not influenced by parental age or newborn sex and suggest that pregnancy and the postnatal period are the most at-risk periods.

Studies of AP and ADHD have also included reports of both positive and null associations. A recent meta-analysis of studies published through December 2018 (27) noted that 9 of 12 studies found positive associations between PM exposures and ADHD, although a high risk of bias was noted. Since then, a prospective study in Taiwan (708,515 families) reported that prenatal AP exposure was associated with childhood hyperactivity disorder in children diagnosed before 8 years of age (28); a study in Korea reported that across a total of 7,200 ADHD- related hospital admissions over 2 years, short term exposures to PM_{10}, NO_2 (considered a marker of traffic), and SO_2 were considered positive risk factors, particularly in those 15–19 years of age compared to 10–14 years of age (29). In a large Canadian prospective study of 37,000 births with 1,217 ADHD diagnoses, incidence of ADHD was increased in relation to levels of $PM_{2.5}$ (30).

Positive associations between SCZ and AP have also been suggested. A meta-analysis focused on hospital admissions for psychiatric care (SCZ, mental disorder, mental and behavioral disorder, panic attack, depression) reported positive associations across 19 studies for multiple metrics of AP exposure, with the strongest associations being with PM_{10} (13 of 16 studies) and $PM_{2.5}$ (8 of the 12 studies) exposures (31). A retrospective cohort study in London of 13,887 individuals found associations between multiple metrics of AP exposures and mental health service use among individuals 15 years of age or older with first presentation of psychotic disorders (32). Recent studies from China specifically related to SCZ reported an increased relapse risk or risk of hospitalization for SCZ in relation to $PM_{2.5}$/PM_{10} exposures in a cohort of 6,220 hospital readmissions (33). A Danish study that included 230,884 individuals, with 2,189 diagnosed with SCZ, found associations between NO_2 and development of SCZ, particularly in men exposed between birth and 10 years of age (34).

4.2. Epidemiological Studies and Meta-Analyses of Neurodegenerative Diseases

AP has also been associated with NDGDs, including AD, PD, and MS (35). Studies of AD/dementia associations with AP include several recent meta-analyses. An analysis that included 9 studies with a population size exceeding ten million 30–85-year-olds across the United States, the United Kingdom, Canada, Spain, Italy, Sweden, and Taiwan found that each 10 $\mu g/m^3$ in $PM_{2.5}$ was positively associated with increased AD risk (odds ratio of 1.95) (36). Another meta-analysis of 4 studies (from Canada, Taiwan, the United Kingdom, and the United States) selected based on a longitudinal cohort study design, with no overlap in study population, a population aged 50 years or older, accessibility of detailed descriptions of $PM_{2.5}$ exposure assessment, and clear definitions of dementia that included more than 12 million people, found that a 10-$\mu g/m^3$ increase in $PM_{2.5}$ was positively associated with dementia (odds ratio of 3.26) as well as with AD (odds ratio of 4.82) (37). Earlier analyses have also provided support for an association of AP with AD/dementia (38, 39).

A meta-analysis of the association of AP with PD that included 9 studies based on $PM_{2.5}$ and 6 studies based on PM_{10} in which sample sizes ranged from 126 to 9,817,806 (median 53,219), the number of PD cases ranged from 72 to 119,425 (median 509), and exposure durations ranged from 2 to 22 years (median 7) (40) also found marginally significant

increases in risk ratios for increases of 10 μg/m^3 in $PM_{2.5}$ (risk ratio of 1.8) but not for PM_{10}. Similarly, a meta-analysis based on 13 studies likewise reported a small increase in relative risk of 1.06 in populations with the number of PD cases ranging from 104 to 9.8 million (41), while a significant increase was reported in another meta-analysis based on seven studies prior to 2017, with an odds ratio of 1.34 (38). A subsequent retrospective cohort study in Korea of 338 individuals with newly diagnosed PD found that comparisons of highest versus lowest quartile of NO_2 exposure increased the hazard ratio for PD (1.41), but no statistically significant associations were found with either $PM_{2.5}$ or PM_{10} (42). In contrast, a prospective cohort study in China with 47,516 participants found a significant increase in PD risk (hazard ratio of 1.5) per each interquartile range increase in $PM_{2.5}$ (43). In addition, a positive nonlinear $PM_{2.5}$–PD association (measured for first hospitalization) was shown to plateau at 11 μg/m^3 in a study in New York state that included 264,075 cases of AD and 114,514 cases of PD (44). As noted in that study, average annual $PM_{2.5}$ concentrations averaged 8.1 μg/m^3, a value below current national US standards. In the largest study to date, that is, a longitudinal cohort study in the contiguous United States of a population of more than 63 million individuals of age 65 or older with over 1 million cases of PD, each 5-μg/m^3 increase in annual $PM_{2.5}$ concentrations was associated with a significant hazard ratio of 1.13 (45).

Inconsistent associations have been reported for MS, and the most recent meta-analysis included 10 studies, based on criteria of being either a case-control, cross-sectional, or cohort study with definite PM diameter, that examined MS relapse and incidence (46). Risk ratio across all studies, where population sizes ranged from 52 to 9,72,756, revealed a significant correlation between $PM_{2.5}$ and PM_{10} with MS incidence and relapse. In addition, a meta-analysis based on the three included studies of $PM_{2.5}$ revealed a significant association. Another recent meta-analysis of six studies with MS case numbers ranging from 424 to 9,247 found an association of PM_{10} but not $PM_{2.5}$ with MS (47). However, in a study in Israel of 287 MS patients, $PM_{2.5}$ was associated with MS relapses in nonsmoking subjects (48), while in a study of 1,246 hospitalizations in France, $PM_{2.5}$ concentration at 3 weeks prior to hospitalization was significantly associated with risk of hospitalization for MS relapse (49). In a study of 1,435 MS patients in Padua, Italy (50), MS prevalence was strongly correlated with the annual average $PM_{2.5}$ concentration.

5. PATHOLOGICAL EVIDENCE FOR A ROLE OF AIR POLLUTION IN NEURODEVELOPMENTAL DISORDERS AND NEURODEGENERATIVE DISEASES

5.1. Brain Pathology and Developmental Air Pollution Exposures

Studies have also begun to evaluate pathological changes in the brain in children in response to developmental AP exposures, primarily via magnetic resonance imaging (MRI), with results that not only further confirm effects of AP on the developing brain but also provide evidence of changes consistent with known brain changes in NDDs. For example, a study of 332 US African-American or Dominican youth from 6 to 14 years of age reported associations of $PM_{2.5}$ with thinning of dorsal parietal cortices, thickening of postero-inferior

and mesial wall cortices, reduced white matter volume, disorganization of white matter in internal capsule and frontal lobe, and increased *N*-acetyl-L-aspartate concentrations in frontal lobe. Interestingly, the authors note the collective impacts in particular on the cortico-striato-thalamo-cortical circuitry connecting frontal, temporal, and parietal cortices with basal ganglia nuclei and thalamus, circuitry implicated to date in multiple NDDs, including SCZ (51) and ADHD (52), with observed effects greater in boys (53).

A study that included four different sites in the United States and China found AP to be related to the progression of hippocampal atrophy after a first episode of SCZ (54). An extensive assessment in 3,133 preadolescents in Rotterdam (55) reported that AP exposures during pregnancy were associated with increased volumes of cerebellum, putamen, pallidum, and amygdala and with reduced volumes of corpus callosum and hippocampus; AP exposures during childhood likewise resulted in reductions in volumes of corpus callosum and hippocampus. Reductions in corpus callosum size in response to $PM_{2.5}$, particularly during pregnancy, have been reported in other studies in children as well (56). A recent examination of 10,343 9–10-year-old children observed hemisphere-specific differences in brain structure in response to $PM_{2.5}$, with, for example, reductions in volume of the left but not right hemisphere nucleus accumbens (57), even at $PM_{2.5}$ exposure concentrations (1.72–15.9 $\mu g/m^3$) that are generally lower than the US Environmental Protection Agency regulations (12 $\mu g/m^3$). $PM_{2.5}$ exposures during the first year of life were associated with reduced gray matter volumes in the left pre- and postcentral gyri and cerebellum and inferior parietal lobe in 135 12-year-olds (58). A study examining elemental carbon and NO_2 as a marker of vehicle exhaust reported alterations in functional connectivity in 263 8–12-year-old children (59), specifically weaker functional connectivity of the default mode network between medial frontal cortex and angular gyrus but stronger functional connectivity between the medial frontal cortex seed region of the default mode network and frontal operculum. Opposite effects were found when functional connectivity was assessed by children's age or motor response speed, suggesting that AP slows brain maturation.

Another study assessed the role of Cu contamination in $PM_{2.5}$ as a potential source of adverse effects. Cu, while required for brain development, is toxic in excess (60). Cu in $PM_{2.5}$ was associated with increased gray matter and lower white matter concentrations in basal ganglia, without an effect on tissue volume. Functional MRI analyses revealed a reciprocal reduction of functional connectivity between the caudate nucleus and operculum of frontal lobe, consistent with anatomic findings. Correspondingly, these effects of Cu were associated with poorer motor performance in children, effects that remained significant following adjustment for several other elements, including carbon, Pb, Fe, and antimony.

5.2. Brain Pathology in Adults

Studies of brain pathology likewise provide further support for a role of AP in NDGDs. Several studies indicate vulnerability of white matter. In a study of 1,302 normal, aging US women without dementia, an increase of 3.22 $\mu g/m^3$ in $PM_{2.5}$ was associated with significantly lower white matter volume in total brain and in temporal lobe and corpus callosum (61), findings consistent with a prior report by these authors (62) of reduced white

matter but not gray matter volume in women without dementia, with findings independent of geographical region, demographics, socioeconomic status, lifestyle, or cardiovascular risk factors. Further, in a study of 8,600 participants from the United Kingdom averaging 55.6 years of age, $PM_{2.5}$ exposure was negatively associated with white matter volume, an effect that was actually exacerbated by vigorous physical activity (63).

Other studies report associations of AP with gray matter volume changes as well. In the study of 8,600 participants from the United Kingdom discussed above, $PM_{2.5}$ exposure was negatively associated with both gray matter and white matter volume. Another study from the United Kingdom of 18,278 individuals averaging 62 years of age found an inverse association of left hippocampal volume with $PM_{2.5}$ (64). A study of 212 participants from Barcelona revealed higher gray matter volume in cerebellum and white matter volume in the splenium of corpus callosum, the superior longitudinal fasciculus, and cingulum cingulate gyrus (65). In a study of 957 participants of an average age of 67 years from four cities in the Republic of Korea (66), PM_{10} exposures were negatively associated with thickness of the frontal and temporal lobes, as well as with reductions in volume of the pallidum, hippocampus, amygdala, and nucleus accumbens, while $PM_{2.5}$ exposures were associated with reduced temporal cortex thickness, but with increases in the occipital and cingulate cortices, and with reductions in nucleus accumbens volume, with generally stronger impacts in men. In a sample of 1,364 women aged 71–89 years, $PM_{2.5}$ was associated with reductions in cortical gray matter volume, particularly in the bilateral superior, middle, and medial frontal gyri (67).

In a study of 615 participants with an age range of 55–85 years, AP was associated with language and short-term memory deficits and with atrophy of the fronto-parietal network, which is associated with these cognitive processes in both sexes, specifically in the right hemisphere. In a compelling longitudinal study (68) of 998 women aged 73–87 years who were given brain scans separated by approximately 4 years, $PM_{2.5}$ was associated with greater reductions in both immediate recall and new learning, such that each increment of 2.81 $\mu g/m^3$ of $PM_{2.5}$ accelerated the annual decline rate in immediate free recall new learning by 14.8–19.3%. Importantly, long-term $PM_{2.5}$ exposures increased the AD pattern similarity scores, an MRI-derived neuroanatomical risk measure for AD.

Brain infarcts have also been associated with AP. In a study of 1,400,503 participants aged 18 years or older from 174 cities in China, each standard deviation increase in AP was associated with a 16–42% increase in the risk of brain infarct (69). Similarly, covert brain infarcts were reported in a population of 943 individuals with a mean age of 68 (70).

6. ANIMAL MODELS EXAMINING THE ROLE OF AIR POLLUTION ON THE BRAIN

In the discussion of animal models in this section, studies employing inhalation exposures are highlighted, as methods such as intranasal or intratracheal instillation do not fully capture important chemical modifications in inhalation exposures. While gases in AP, for example, ozone and SO_2, have also received attention, this literature is currently far less expansive and consequently is not included here. The studies summarized below are selected

highlights, but a more extensive review of inhalation studies in animal models is provided in Supplemental Tables 1 and 2.

6.1. Developmental Exposure Models

Studies of inhalation exposures during the periods encompassing brain development in experimental animals, while limited to date, support the vulnerability of the developing brain to AP and provide biological plausibility for the epidemiological studies (see Supplemental Table 1). Studies from our laboratory have examined the impact of concentrated ambient fine-particle/UFP exposures during gestation (6 h per day from gestational day 0.5 to 16.5) (71, 72), as well as concentrated ambient UFP exposures during early postnatal development in the mouse (73–77), which mirrors human third-trimester brain development (78). Observed effects were dependent upon the developmental period of exposure, offspring sex, and brain region. Gestational exposure increased corpus callosum size and produced premature and excessive myelination in both offspring sexes at postnatal day (PND) 14, consistent with a shift toward a more activated microglia state and a more mature oligodendrocyte phenotype in corpus callosum (71). These exposures also slightly (approximately 10%) but significantly reduced mean hippocampal area but did not alter frontal cortical thickness. All effects occurred in the absence of any maternal or offspring overt toxicity (72). Ventriculomegaly persisted in females but not in males in adulthood, while increased corpus callosum area and myelination persisted in both sexes. Notably, increases in levels of Fe, a primary driver of myelination (79), were found in the female but not male corpus callosum, and these levels correlated significantly with increases in myelin density, while increased Fe concentrations were found in cerebellum of both offspring sexes (80).

Postnatal exposures of mice to concentrated ambient UFP were carried out on PND 4–7 and 10–13 for 4 h per day, a period of very high rates of both neurogenesis and gliogenesis (81) and, as expected given differences in ongoing brain development at the time of exposure (75–77), produced different neuropathological consequences. Male-specific and persistent ventriculomegaly was seen even at PND 270. Male-specific reductions in corpus callosum size and myelination were seen at PND 14 but resolved by PND 270. Effects in corpus callosum were most pronounced in the truncus and medial external capsule, regions that were under development at the time of exposures. Striatal myelination was not affected, consistent with its development after the exposure window used in these studies. Male-specific and persistent excitatory-inhibitory glutamate imbalance was observed in frontal cortex, and 340% increases in microglial activation were seen in male corpus callosum at PND 270. Behavioral features included male-biased impulsivity, cognitive inflexibility, and reduced social novelty preference (73, 82). In another study, postnatal exposures of mice to inhaled $PM_{2.5}$, albeit at very high exposure concentrations, likewise resulted in reductions in corpus callosum size, although sex differences were not considered in the study (83).

Aerosolized resuspended nanoparticulate matter exposure (340 $\mu g/m^3$) in rats from development to adulthood reduced neurogenesis in dentate gyrus and produced glial activation, hippocampal Fe deposits, and microbleeds, coupled with behavioral deficits in impulsivity and impaired short-term memory (84). MRI examination in male rat offspring

exposed during gestation and lactation to $PM_{2.5}$ in a traffic tunnel at concentrations of approximately 200 $\mu g/m^3$ revealed decreased structural integrity of gray matter in anterior cingulate as well as hippocampus, in addition to cognitive and social behavioral deficits (85). Direct exposures to ambient AP during gestation and early postnatal development produced sex-dependent differences that included increased hippocampal neurogenesis in males and increased granular cell layer width and reduced lateral ventricle volume in females (86). No systemic toxicity was found in any of these studies. Neurons derived from offspring cerebral cortex at 24 h showed an increase in undifferentiated neurons but no reduction in total numbers of neurons following prenatal exposure (87) of mice to reaerosolized urban nanoparticles (350 $\mu g/m^3$) for 5 h, 3 times per week for 10 weeks, including gestation.

Another series of studies examining developmental exposures of mice to 250 $\mu g/m^3$ diesel exhaust PM from embryonic day 0 through weaning reported alterations in levels of transcription factors relevant to neurogenesis in whole brain at PND 3 in male offspring and reductions in neurogenesis in the subgranular zone of hippocampus at PND 60 in both sexes (88). Earlier studies by this group reported increases in IL-6 in placenta and the fetal brain, as well as downregulated expression of reelin (RELN), critical to neuronal migration (89). Studies of diesel exhaust at lower concentrations have reported more limited but male-specific neurotoxicity, consisting of increased inflammation in corpus callosum and cortex, but no changes were found in behavioral function (90). Deficits in elevated plus maze and water maze performance and altered levels of hippocampal glutamatergic receptors have also been reported after exposures of mice to higher levels (350–400 $\mu g/m^3$) of diesel exhaust (91).

6.2. Adult Exposure Models

An even more extensive literature has emerged examining AP exposures in adult animal models (see Supplemental Table 2). Inhalation exposures of adult male mice to resuspended nanoparticulate matter increased microglial activation and produced white matter injury and axonal degradation in corpus callosum (92). A 14-month exposure to ambient $PM_{2.5}$ in a tunnel in northern California of TgF344-AD rats that express human AD risk genes or normal, wild-type littermates increased amyloid deposition, hyperphosphorylated tau levels, and neuronal loss while also producing cognitive deficits, with effects being age, genotype, and sex dependent (93). A 4-week exposure of male mice to ambient AP (28 ± 8 $\mu g/m^3$) in a highly polluted area of Buenos Aires produced mitochondrial dysfunction and increased oxidant production (94). Interestingly, chronic exposure of male mice to ambient $PM_{2.5}$ with an average concentration of 16.32 $\mu g/m^3$ (95) suggested a preferential vulnerability of cortex relative to striatum, with increased numbers of neurons and microglia; such effects partially reversed following cessation of exposure. Exposures of APP/PS1 mice, another genetic model of AD, to average $PM_{2.5}$ levels of 25.8 $\mu g/m^3$ increased hippocampal Aβ plaque load as well as microgliosis and astrogliosis (96). An interesting study of exposure of male mice to ambient $PM_{2.5}$ for 3, 6, 9, or 12 months at concentrations ranging from 17 to 57 $\mu g/m^3$, while showing cognitive deficits only at the 9-month time point, did reveal increases in both astroglial and microglial activation across exposure periods (97).

A 9-month exposure of C57Bl6J male mice to inhaled concentrated ambient $PM_{2.5}$ (concentration of 65.7 ± 34.2 μg/m3) increased protein levels of the beta-site amyloid precursor protein cleaving enzyme (BACE), amyloid precursor protein (APP) processing, and Aβ1–40 levels, while decreasing APP levels, but it did not influence tau and produced no significant inflammation. While the findings suggest an impact of $PM_{2.5}$ on Aβ pathways, increases in BACE and Aβ1–40 levels would not necessarily increase APP processing, as noted by the authors, so further studies are warranted to better understand the pattern of outcomes.

Two studies have examined specific components of AP in relation to AD-like neuropathology. Male C57Bl6J mice were exposed to 0, 2.5, or 5.0 mg/m^3 NO_2 for 5 h per day for 4 weeks in a whole-body inhalation chamber (98). The high NO_2 concentration increased phosphorylated tau protein expression in both cortex and hippocampus, reduced glutamate receptor expression, and produced thinner postsynaptic densities, consistent with impaired synaptic function.

Diesel exhaust adult models have also been developed. A 14-week diesel exhaust exposure produced a male-biased increase in neuroinflammation and oxidative stress (99), while in another study, exposures of rats to either 200 or 1,000 μg/m^3 produced both microglial and astrocytic activation (100). Diesel engine exhaust exposure for 6 h per day, 5 days per week for either 3 or 13 weeks (101) in female 5X familial Alzheimer's disease mice increased cortical Aβ plaque formation and Aβ42 following the 3-week but not 13-week exposure, a finding the authors attributed to a ceiling effect. Adult rats (sex not specified) exposed to ambient $PM_{2.5}$ for 24 h per day, 7 days per week for 12 weeks (average of 44 μg/m^3), but not 6 weeks (average of 27 μg/m^3), showed increased middle cerebral artery narrowing and expression of multiple proinflammatory cytokines.

Experimental animal studies have also begun to address neuronal atrophy, impaired neurogenesis, and impaired synaptic function. In one such study (102), young (3 months old) or aged (18 months old) female C57Bl6J mice were exposed to resuspended traffic-related nanoparticles for 5 h per day, 3 days per week for a period of 10 weeks (342 ± 49 μg/m^3) which resulted in the young but not old mice showing selective increases in neurite atrophy and reduced myelination in hippocampal CA1 regions. The absence of effect in aged females was attributed to a possible ceiling effect, and the selective effect on CA1 was considered to be of interest given its vulnerability in AD (103). Effects of acute $PM_{2.5}$ diesel exhaust exposure (a single 6-h exposure) in adult mice at a concentration of 250–300 μg/m^3 found a male-specific reduction in neurogenesis in the hippocampal subgranular zone, subventricular zone, and olfactory bulb (104), effects that could be mitigated by blocking microglial activation.

7. HOW COULD AIR POLLUTION INFLUENCE RISK FOR SUCH A WIDE ARRAY OF NEURODEVELOPMENTAL DISORDERS AND

NEURODEGENERATIVE DISEASES? SHARED FEATURES AND MECHANISMS

As the above discussion indicates, an accumulating body of epidemiological, pathological, and experimental evidence links AP exposures to multiple NDDs and NDGDs. One question raised by this collective evidence is how AP could influence so many different NDDs and NDGDs. While research typically focuses on the differences between various NDDs and NDGDs, it is actually the case that they share numerous mechanisms of injury and pathological characteristics (shared outcomes), which may be corresponding targets of AP (Figure 1).

Inflammation and microglial activation are considered etiological factors in both NDDs and NDGDs (105, 106), thus constituting shared mechanisms of injury in these disorders. Similarly, AP is an inflammatory stimulus, as has been repeatedly documented for cardiopulmonary systems (107) and more recently seen in studies of AP (108) and associated experimental animal models (109). Thus, AP-induced inflammation may serve as a mechanism that sets off other upstream effects or converges on shared downstream outcomes, such as white matter damage, that underlie both NDDs and NDGDs.

Another hypothesized mechanism of injury attributed to both NDDs and NDGDs is mitochondrial dysfunction (110), and studies of AP's effects on the brain are also demonstrating its adverse impact on mitochondrial function (94, 111); indeed, UFPs have been found in mitochondria of the brain and heart biopsies of Mexico City inhabitants who were chronically exposed to AP (112). Whether such effects reflect direct effects on mitochondria or are a response to AP-related inflammation is not yet known.

Alterations in glutamatergic function are also prominent in NDDs and NDGDs (113–115). Alterations in brain glutamatergic function have been reported in both developing and adult exposure models of AP (77, 116–118). Glutamate has multiple roles in the brain, including regulation of induction of synapses and their interconnection with astrocytes, cell migration, synaptic spatial organization of the cerebellum, cell differentiation, and apoptosis. Excess glutamate is an excitotoxin that can result in lipid peroxidation as well as neuronal dysfunction, white matter damage, and degeneration.

As exemplified in Figure 1, multiple mechanisms of injury known to be triggered by AP could converge on white matter damage, an outcome shared across NDDs and NDGDs (119, 120). White matter alterations also appear to be a prominent target of AP. Of particular note, in a study of 186 8–12-year-old children who underwent brain MRI, increased $PM_{2.5}$ during the third trimester of pregnancy was associated with both a reduction in the corpus callosum volume and a higher hyperactivity score, although statistical significance did not survive correction for multiple comparison (56). Nevertheless, such findings are remarkably similar to those reported in animal models following early postnatal (human third trimester brain development equivalent) exposures to concentrated ambient UFPs that likewise showed reductions in corpus callosum size accompanied by hypomyelination (75). To date, alterations in white matter, particularly reductions in volume and other features,

seem to be the most frequently reported change in human MRI studies, in both children and adults (53, 55, 56, 61–63).

Another example of a shared outcome is ventriculomegaly (enlarged lateral ventricles), which are reported in studies of both NDDs and NDGDs (121, 122). While assessment of lateral ventricle size in animal studies of AP exposure has been quite limited to date, it has been reported in response to UFP exposures during the early postnatal period (equivalent to human third trimester brain development), which in the case of developmental exposure was male biased and appeared to persist over the lifetime (75). Whether adult AP exposures either produce or further increase lateral ventricle size remains to be determined.

8. AIR POLLUTION AND BRAIN METAL DYSHOMEOSTASIS

As noted above, PM is a source of adsorbed contaminants, including metals and trace elements, that directly enter the brain via nasal olfactory uptake, thereby bypassing the blood-brain barrier. Levels of Fe, Al, and silicon are among the highest in AP, with lesser levels of S, Zn, Pb, and Cu. Correspondingly, our studies of inhaled ambient UFPs during the postnatal period revealed pronounced changes in brain metal content, with marked increases in Fe, S, Cu, and calcium (Ca) and to a lesser extent Al, at the expense of Mn and Zn (123).

Of particular note with respect to exposures to inhaled metals is the well-documented increase in brain Fe in many major NGDGs. Fe is known to accumulate in the brain with normal aging, but excess levels occur in NDGDs such as AD, PD, and MS (124, 125) and can underlie ferroptosis, a mechanism of cell death produced by increased Fe and associated oxidative stress and lipid peroxidation (126). Such increases are often hypothesized to reflect alterations in the brain, changes in peripheral Fe metabolism, aging-related pathophysiological changes in barriers such as the blood-brain barrier, or changes in the gastrointestinal tract as sources of increased brain Fe (21).

However, the possibility that life-long exposures to metals via AP underlie these increases and lead to brain metal dyshomeostasis does not appear to have been considered. It would be particularly interesting to consider the nasal olfactory uptake of AP contaminants via olfactory and trigeminal nerves in relation to Braak staging for AD and PD (127–129). It has been proposed that PD originates at two sites, that is, the olfactory bulb and medulla oblongata (brainstem), via vagal nerve interconnections; AD staging has highlighted the entorhinal region located between hippocampus and the transentorhinal region as an initiation point. These are regions that receive olfactory nerve input (127) that would then contain AP contaminants that move into allocortex (olfactory bulb, entorhinal cortex, and hippocampus). In addition, potential vagal nerve retrograde transport into the brainstem from PM circulating in the bloodstream may be occurring, although the latter has yet to be examined.

Correspondingly, studies have demonstrated inflammation in olfactory epithelium in response to AP (130), as well as human olfactory-brain uptake of inhaled UFPs (131). For example, olfactory bulbs of mice exposed intranasally to 14 nm of carbon black particles for

4 weeks exhibited elevated messenger RNA levels for multiple markers of cytokine activity and inflammation; such inflammation can influence various cognitive behaviors (132). Repeated intranasal instillation of lipopolysaccharide, an inflammatory model, produced olfactory bulb atrophy and olfactory sensory neuron degeneration (133).

In addition to increased Fe, dyshomeostasis of other metals is also seen in AD (124), including reductions in Cu (despite concurrent increases in Cu in serum/plasma) (134) and disruptions in Zn concentrations (135). Ca, also a contaminant of PM, can impair lung (136) and cardiac function (137). While the potential impact of elevated Ca from AP on brain function has yet to be considered, it is notable that postnatal exposure of mice to concentrated ambient UFPs markedly increased brain Ca levels in addition to Fe and Cu (138). The toxicity of excess Ca in the brain in relation to AD has long been known (139).

While metal/elemental disturbances have likewise been reported with NDDs (140), much of the focus of this literature has been on serum metal levels, which may not reflect brain metal levels. For example, alterations in trace metals levels in serum or in hair or nails are reported and sometimes correlated with features or severity of ASD (141); the observed metal profiles can differ by sex (142) and geographic location. Alterations in brain metal levels in ASD have been reported (143, 144) as have correlations of trace metal levels with neuroinflammatory markers (145). Similar findings are reported in SCZ, particularly for Zn and Cu (146, 147), as well as in ADHD (148). Interestingly, however, a recent meta-analysis of studies in children with ADHD found an inconsistent association of systemic Fe with ADHD, whereas a significant association was found between reduced brain thalamic Fe and ADHD (149).

9. THE DECLINE IN AIR POLLUTION DOES NOT INCLUDE UFPS

Another important question is how increasing prevalence of NDDs and NDGDs could be associated with AP exposures when AP levels are being regulated and have declined. It has been assumed that regulation of PM_{10} and $PM_{2.5}$ levels would also reduce levels of UFPs, considered the most toxic component of AP. However, it now appears that $PM_{2.5}$ and UFP levels are actually not correlated (150), likely due to a lower $PM_{2.5}$ level reducing the scavenging of UFPs. Thus, regulating $PM_{2.5}$ concentrations does little to reduce UFPs (150). This finding raises significant questions as to the adequacy of current regulations and may also explain why, even with cleaner air (by mass), AP could continue to contribute risks for NDDs and NDGDs.

10. FUTURE RESEARCH NEEDS FOR ADVANCING THE UNDERSTANDING OF THE ATTRIBUTABLE RISK OF AIR POLLUTION ON NEURODEVELOPMENTAL DISORDERS AND NEURODEGENERATIVE DISEASES

A critical need to further our understanding of the contribution of AP to NDDs and NDGDs is the development/implementation of in vivo animal models of inhalation exposures. Nonphysiological bolus-type instillation exposures are quite disparate from

ambient exposures in terms of chemistry, dose-rate, and absence of deposition in the respiratory tract. It is important to note that UFPs form protein coronas on biological substrates, the nature of which can influence their targets and ultimate impact. Furthermore, the protein corona is not static; its composition evolves as UFPs travel, such as when crossing the blood-brain barrier, meaning that the initial composition is not predictive of fate and effects after it crosses the blood-brain barrier (151).

An additional need is assessment of the role of specific contaminants in producing the associated neurotoxicity, a need underscored by the reports of metal dyshomeostasis in both groups of diseases and disorders. As noted above, metal and trace element contaminants are one such class of potential toxicants. Organic contaminants are another possibility, as demonstrated by correlations of polycyclic aromatic hydrocarbons with reductions in white matter in human studies (152). In addition, AP contamination can include endotoxins (153), which is notable as lipopolysaccharide is an inflammatory stimulus used to model NDDs and causes delayed myelination, neuronal loss, and cerebellar hypoplasia following neonatal administration (154). While this review has focused on PM toxicity, gases such as SO_2 and H_2S are also a component of AP. For example, an increased odds ratios for ASD was found for several gaseous components of AP (155), with effect estimates of a 59%, 37%, and 340% risk increase per 10-ppb increase in ozone, CO, and NO_2 levels (95% confidence interval 3.31–5.85), respectively, and 17% per 1-ppb increase in SO_2 level. SO_2 exposures during pregnancy and in the first 12 months postnatally were also associated with poor subclinical neurodevelopment, primarily deficiencies in fine motor behavior following adjustment for relevant covariates (156). Further assessments of the potential for these contaminants to phenocopy NDDs and NDGDs provide information that is not only highly relevant to mechanisms of NDDs and NDGDs but, when coupled with concentration response functions, also relevant to potential regulatory actions. The inclusion of both sexes in such studies is also requisite to understanding mechanisms that underlie the sex differences seen in NDDs and NDGDs.

As of yet, the current understanding of the impact of AP exposure timing and duration is limited. With respect to brain development, studies of exposures during specific trimesters are important but to date have been mostly pursued in epidemiological studies. In the case of NDGDs, several additional questions need consideration. For example, can developmental exposures, perhaps via fetal programming, ultimately set conditions of vulnerability to NDGDs, that is, consistent with a fetal basis of adult disease hypothesis? Or do NDGDs arise from adult exposure, and, in either case, must these exposures be sustained or episodic?

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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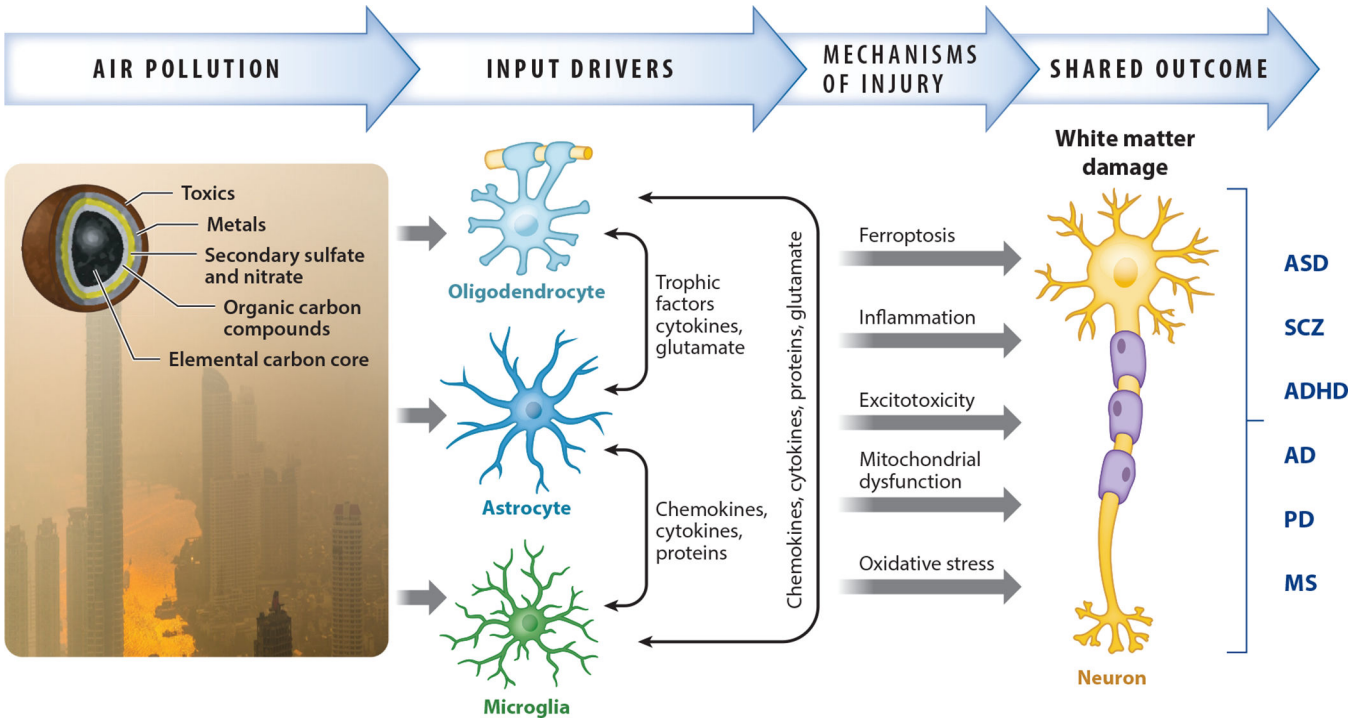

Figure 1.

Schematic example of how mechanisms of neurotoxicity produced by central nervous system exposures to air pollution, a complex mixture of gases and particulate matter with adsorbed organic and inorganic contaminants, can lead to a pathological feature such as demyelination that is shared across NDDs and NDGDs. Via its effects on multiple cell types in the brain and their interactions, air pollution leads to various mechanisms of injury, which are also shared across NDDs and NDGDs, that underlie such outcomes. Photo by Peggy Anke on Unsplash. Abbreviations: AD, Alzheimer's disease; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; MS, multiple sclerosis; NDD, neurodevelopmental disorder; NDGD, neurodegenerative disease; PD, Parkinson's disease; SCZ, schizophrenia.