Review

Outdoor air pollution and brain development in childhood and adolescence

Megan M. Herting [1,*], Katherine L. Bottenhorn[1,2], and Devyn L. Cotter[1,3]

Exposure to outdoor air pollution has been linked to adverse health effects, including potential widespread impacts on the CNS. Ongoing brain development may render children and adolescents especially vulnerable to neurotoxic effects of air pollution. While mechanisms remain unclear, promising advances in human neuroimaging can help elucidate both sensitive periods and neurobiological consequences of exposure to air pollution. Herein we review the potential influences of air pollution exposure on neurodevelopment, drawing from animal toxicology and human neuroimaging studies. Due to ongoing cellular and system-level changes during childhood and adolescence, the developing brain may be more sensitive to pollutants' neurotoxic effects, as a function of both timing and duration, with relevance to cognition and mental health. Building on these foundations, the emerging field of environmental neuroscience is poised to further decipher which air toxicants are most harmful and to whom.

Neurotoxicity of ambient air pollution: a public health concern

Ambient air pollution is nearly ubiquitous and is considered one of the greatest environmental threats to human health [1]. As a complex mixture of gases and small particles, air pollution arises from both natural and anthropomorphic sources, most notably from vehicle exhaust and industrial emissions [2]. Air pollution varies geographically, comprising both primary and secondary substances. Primary pollutants are emitted directly from a source, whereas secondary pollutants are formed from primary pollutants reacting in the atmosphere [2]. The World Health Organization (WHO) has assigned standard limits for six ambient air pollutants, above which concentrations are considered harmful to human health[i] (Table 1). These include particulate matter (PM) of different size fractions ($PM_{2.5}$, PM_{10}), nitrogen dioxide (NO_2), ground-level ozone (O_3), carbon monoxide (CO), sulfur dioxide (SO_2), and lead (Pb). The WHO further considers black carbon, ultrafine particles (UFPs), and mold as harmful air pollutants due to their potential health effects, though they lack recommended standards. Despite policy and public health guidelines, both national and global, exposure to hazardous levels of air pollution still occurs in megacities worldwide [3] and elsewhere. Indeed, 99% of people – almost the entire global population – are estimated to regularly breathe air of worse quality than the WHO's recommendations[i] [4]. Epidemiological studies have increasingly reported various adverse health effects, even at concentrations within current standards [5,6]. Among the pollutants studied, the current literature suggests that ambient fine-particle pollution – $PM_{2.5}$, ≤2.5 μm in diameter, which includes UFPs (≤100 nm in diameter) and nanoparticles (nPM, ≤50 nm in diameter) – has the most concerning and potentially detrimental health effects, as smaller particles are able to travel longer geographic distances and infiltrate biological tissue barriers once inhaled [7–9].

Beyond well documented adverse cardiovascular and pulmonary consequences, a growing body of research suggests that air pollution has harmful neurotoxic effects [8,10–14]. Child and

Highlights

Ambient air pollution is ubiquitous and poses a significant public health concern as a harmful neurotoxicant.

During childhood and adolescence, ongoing developmental processes may render the brain especially vulnerable to air pollution.

Primary targets for air pollution neurotoxicity include neurons and glial cells, which have heterogeneous functions that are essential to neurodevelopment.

A growing body of human neuroimaging research shows that exposure to air pollution is linked to changes in brain structure and function in youth.

Given dynamic changes in brain maturation, direction and magnitude of air pollution effects tend to be dependent on timing and brain region.

[1]Department of Populations and Public Health Sciences, University of Southern California, Los Angeles, CA, USA
[2]Department of Psychology, Florida International University, Miami, FL, USA
[3]Neuroscience Graduate Program, University of Southern California, Los Angeles, CA, USA

*Correspondence:
herting@usc.edu (M.M. Herting).

Table 1. Air pollution types, sources, and standards[a,b]

Air pollutant	Sources	WHO recommendations	US EPA standards
Particulate matter with diameter ≤10 μm (PM$_{10}$)	Natural (wind-blown pollen, salt from sea spray, erosion); anthropogenic (farming/agriculture, roadways, factories/mining operations); combustion of fuels; chemical reactions between gases	45 μg/m^3 (24 h) 15 μg/m^3 (1 year)	150 μg/m^3 (1 year)
PM with diameter ≤2.5 μm (PM$_{2.5}$)		5 μg/m^3 (1 year)	9.0 μg/m^3 (1 year)
UFP with diameter ≤0.1 μm (100 nm)		None	None
SO$_2$	Burning of sulfur-containing fuels, such as coal, petroleum, or diesel	40 mg/m^3 (24 h)	75 ppb (1 h)
NO$_2$	Internal combustion at high heats, usually from traffic	25 μg/m^3 (daily average) 10 μg/m^3 (1 year)	100 ppb (1 h) 53 ppb (1 year)
O$_3$	Secondary pollutant created when nitrogen oxides and volatile organic compounds (from motor vehicle exhaust, power and chemical plants, factories, refineries) react with UV rays from the sun	100 μg/m^3 (8 h) 60 μg/m^3 (24 h maximum in peak season)	0.07 ppm (8 h)
CO	Incomplete/inefficient combustion processes from vehicles (especially from poorly tuned engines), biomass burning, and coal	4 mg/m^3 (24 h)	35 ppm (1 h) 9 ppm (8 h)
Pb	Ore and metal processing; aircrafts that still operate using leaded gasoline	0.5 μg/m^3 (1 year)	0.15 μg/m^3 (rolling 3 month)

[a]Description, source, and global (WHO)[i] as well as US (EPA)[iii] regulatory standards for each pollutant.
[b]Abbreviations: ppb, parts per billion; ppm, parts per million.

adolescent exposure to air pollution is particularly concerning because brain development extends from a few weeks after conception into the second decade of life [15,16]. Herein, we review emerging evidence from both experimental animal studies and non-invasive human magnetic resonance imaging (MRI) studies suggesting that PM$_{2.5}$ may impact the developing brain. We begin with a brief overview of air pollutants' known exposure routes, then highlight how dynamic changes at the cellular, circuit, and system level throughout childhood and adolescence may make the developing brain particularly vulnerable to air pollution. Building on fundamental work in developmental neurobiology and environmental neurotoxicology, we discuss the promise of coupling advanced high-resolution air pollution modeling and human neuroimaging techniques to further elucidate neurotoxic effects of ambient PM$_{2.5}$ in the developing brain. We conclude by discussing recommendations on future research priorities: characterizing long-term consequences and lifetime cumulative effects of exposure, disentangling pollutant 'mixture effects', identifying the most harmful component(s) and source(s) of pollution, and uncovering individual differences in susceptibility to these harmful neurological effects. We argue that neurodevelopmental and system-level processes that continue well into young adulthood may be particularly sensitive to air pollution, depending on exposure timing and duration.

Air pollution: routes of exposure
Particle pollution, or PM, is a complex mixture of solid and liquid droplets with variable sizes and compositions (Table 1) [9]. Depending on its physical and chemical properties, particle pollution

can take various routes to impact the brain. *In utero*, PM may activate maternal inflammation and oxidative stress pathways, while also damaging the blood–placenta barrier [10]. Recent human studies suggest that maternal exposure to black carbon can reach the fetal side of the placenta (Figure 1A) [17,18]. Further, trace elements (e.g., iron, sulfur) and other metals (Pb, copper, etc.) can adhere to particle pollution and cross from maternal to fetal circulation to accumulate in fetal tissue [8]. Postnatally, there are two main routes to the brain: the respiratory and the nasal pathways (Figure 1B) [19]. The respiratory pathway begins with inhaled particles that enter the lungs. Smaller particles can penetrate deeper into the lungs and bypass sentinel immune cells and various biological tissue barriers, making them potentially more toxic [20]. From the lungs, smaller particles can pass through alveoli into the bloodstream, where they may eventually travel to, and infiltrate, the brain [21,22]. PM that enters the lungs and bloodstream may induce peripheral systemic effects, such as inflammation, and harm other organ systems (i.e., endocrine, cardiovascular) [23]. $PM_{2.5}$ has been found in both human cerebral spinal fluid and blood, supporting the potential route from the lungs to the brain via systemic circulation [21]. In the nasal pathway, inhaled UFPs may be directly transported to the brain via the olfactory nerve to the olfactory bulb, or by way of other cranial nerves [24–26].

Child and adolescent brain development: a vulnerable period for air pollution neurotoxicity

Converging evidence from animal inhalation studies suggests several mechanisms of CNS toxicity following air pollution exposure: altered neuron and glial cell morphology and function,
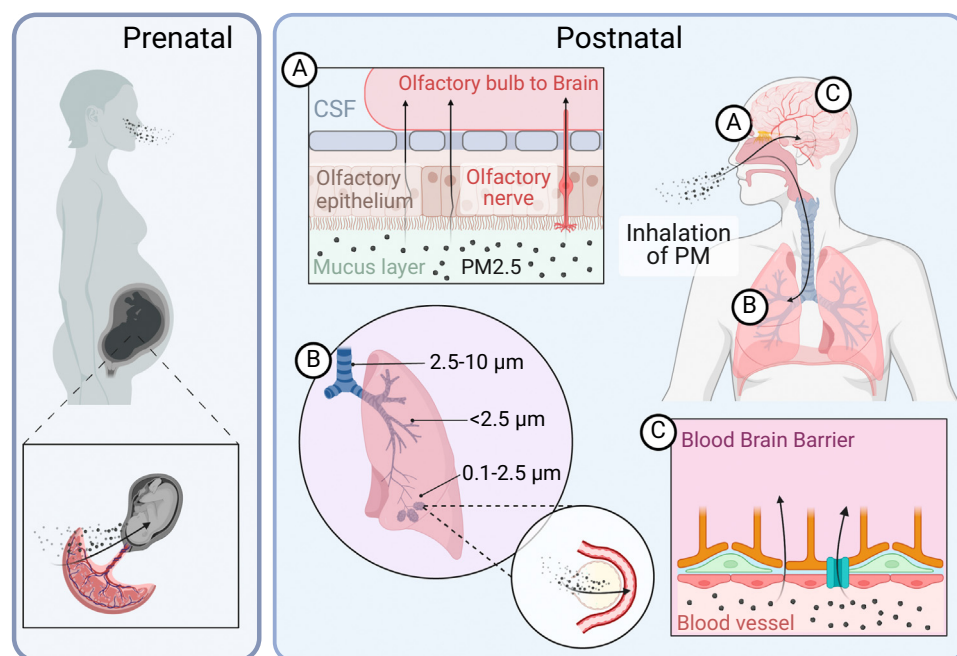

Figure 1. Possible pathways of particulate matter (PM) into the brain. Prenatal exposure (left) can occur following maternal inhalation of PM, which can enter the bloodstream and eventually cross from maternal to fetal circulation. Following inhalation of PM, postnatal exposure (right) can lead to neurotoxicity as pollutants can (A) travel along the olfactory bulb (following nasal inhalation) and crossing the cribriform plate to enter the brain; (B) enter the bloodstream through alveoli in the lungs, which can lead to systemic inflammation; and (C) infiltrate the brain when ultrafine particles (UFPs) cross the blood–brain barrier. Figure created with BioRender.

increased inflammation and oxidative stress, and impaired blood–brain barrier (BBB) integrity [8,10,11,14]. Many of these neurobiological processes are especially in a state of flux during child and adolescent development, plausibly rendering them more vulnerable to long-lasting ramifications of air pollution neurotoxicity. In this article, we briefly review the cellular and system-level changes underlying child and adolescent neurodevelopment, then discuss potential sensitivity of these various processes to PM depending on exposure timing and duration. In doing so, we highlight both animal toxicological findings and emerging evidence from human neuroimaging studies. Lastly, we discuss the potential relevance of neurotoxicant effects of air pollution in understanding risk for cognitive and mental health problems in today's developing youth.

Child and adolescent neurodevelopment

Brain development is a prolonged process that begins *in utero* and continues into young adulthood. Neurulation, cell proliferation, migration, and differentiation during the prenatal period are essential for proper formation of brain structures and their function(s) [27]. Angiogenesis [28] and the formation of the BBB [29] begin prior to birth, and are essential to the brain's vascular network. Formation and refinement of neural connections and networks also commence *in utero* but become especially prominent postnatally. Across early childhood (infancy to age 6 years), mid to late childhood (ages 6–10 years), and adolescence (ages 10–24 years) [30], widespread structural and functional changes in brain plasticity occur hierarchically [31]. Neural synapse proliferation and selective pruning occur sequentially; in terms of brain networks, sensory pathways for basic vision, hearing, and other senses develop first, followed by brain regions involved in early language, and then structures supporting higher cognitive and social functions (Figure 2A) [16]. As these large-scale systems develop, everyday experiences – whether beneficial or harmful – confer continued refinement and adaptation of neural circuitry (i.e., experience-based plasticity), which is especially prominent during childhood and adolescence [32,33]. The underlying cellular and circuit-level changes involve a variety of processes, including neurogenesis, priming and proliferation of glial cells, synaptogenesis, synapse elimination (i.e., pruning), apoptosis, and myelination (Figure 2B) [27,28,34–36]. Many of the processes essential to the rapid expansion, refinement, and reinforcement of efficient brain circuits during development depend on glial cells [27,34,36]. Microglia, although historically labeled the brain's 'resident immune cells', are increasingly recognized as remarkably heterogeneous cells whose function(s) evolve(s) over time to accommodate the needs of the developing brain and, ultimately, help regulate neuronal excitation, plasticity, and circuit formation [36,37]. During development, microglia play an essential role in engulfing dendritic spines as part of the synaptic pruning process, while also supporting myelination, vasculogenesis, BBB permeability, and neuronal function. Microglia consistently respond to their local environment; their state and subsequent function reflect local and transient physiological conditions [37]. While microglia are actively engaged in developmentally-timed synaptic pruning and neurogenesis, their role likely shifts to maintaining homeostasis as brain regions reach an adult-like state [37]. Astrocytes are also involved in synaptic pruning during development and in synapse formation across development and into adulthood [35]. Moreover, astrocytic endfeet are crucial for angiogenesis and BBB development and stability, providing the developing brain with nutrients and offering protection from harmful substances [28,29,35]. Oligodendrogenesis begins prenatally and substantially increases to facilitate cortical myelination as a function of neural demands that increase with age [34]. As myelin may provide a structural barrier to neurite outgrowth, myelination has been hypothesized to function as a 'brake' in brain plasticity. However, oligodendrocyte numbers may continue to fluctuate in response to experience-dependent neural circuitry changes to provide additional support where necessary [38]. The complex interplay of these time-dependent cellular processes ultimately engenders the creation of hierarchically organized neural circuits that underlie cognitive and emotional development that persists across adolescence and into young adulthood.
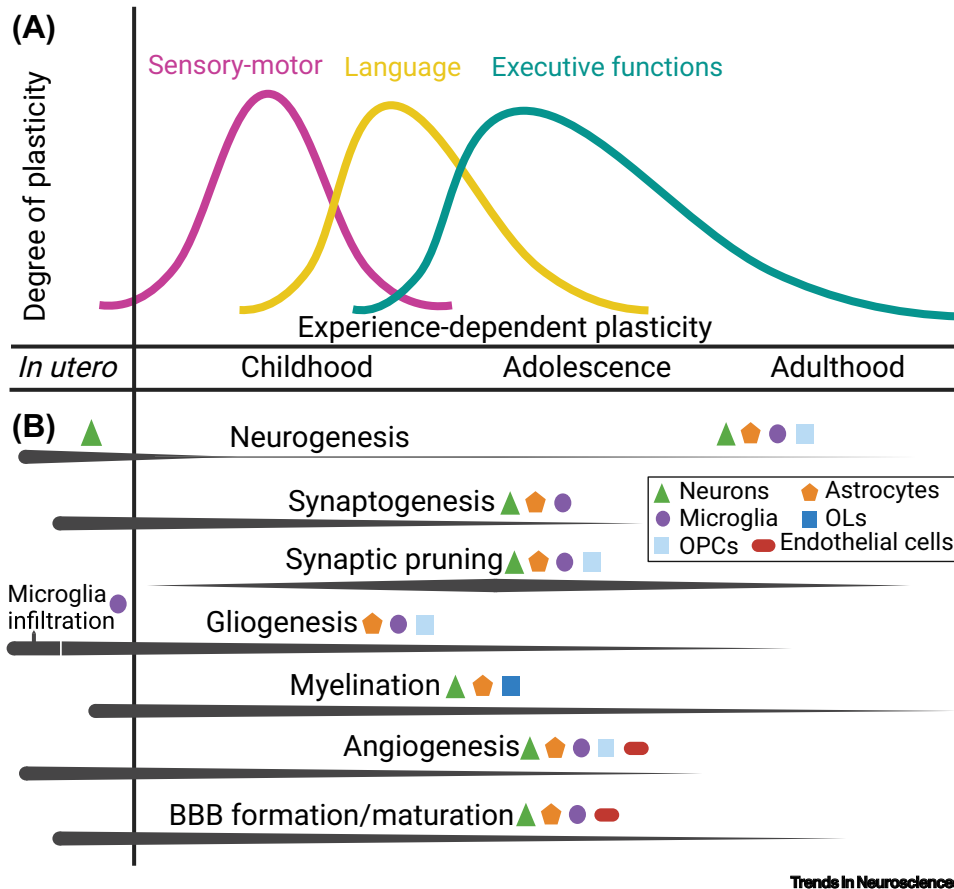
Figure 2. Sensitive periods in human brain development during childhood and adolescence. (A) Neuroplasticity of different functional systems in humans, with approximate timelines adapted from [141]. Sensory–motor development peaks in early childhood, followed by language acquisition which peaks in childhood but continues into early adolescence. Social skills, executive functioning, and emotional regulation develop last, peaking in adolescence and continuing into adulthood. (B) Schematic illustration of approximate timelines for human neurodevelopmental processes across the prenatal period into adulthood as well as the main cells involved in each process (adapted from [142]). Embryonic neurogenesis begins in early gestation and continues through birth, wherein neural progenitors give rise to neurons; postnatal and adult neurogenesis involves astrocytes, microglia, and oligodendrocyte (OL) precursor cells (OPCs), with timelines that are brain-region-dependent [142]. Synaptogenesis – the formation of synaptic connections between neurons to facilitate information transfer – begins at about gestational week 12. Synaptic pruning, whereby existing synaptic connections are selectively eliminated for increased network efficiency, begins in late gestation with increasing levels of activity just after birth and continuing into adolescence [143]. Yet, the timing of both synaptogenesis and synaptic elimination during development varies greatly between cortical regions [144]. Microglial entry into the brain, defined by migration from the ventricular lumen and leptomeninges, occurs approximately between gestational weeks 4 and 16 [145]. Gliogenesis, the generation of glial cells (including oligodendrocytes and astrocytes), begins around gestational week 22 [142]. Glial-mediated myelination in the brain increases significantly around 32 weeks of gestation but progresses well into childhood and adolescence [142], with temporal variance by brain region [146]. Angiogenesis begins around week 8 of gestation and continues postnatally [28]. Formation of the blood–brain barrier (BBB) also begins *in utero*, with some functional barrier mechanisms present as early as gestational week 14 [147]. Physical maturation and functional changes of the BBB also occur postnatally to adapt to the dynamic needs of a specific neurodevelopmental stage [147]. Figure created with BioRender.

Neurotoxic effects of air pollution: evidence from animal models

Emerging literature suggests that air pollution may disrupt neuron–glia interactions, incurring both morphological and functional changes to neurons and glial cells. In doing so, pollutants may cause aberrant myelination, microglial infiltration, oxidative stress, metal dyshomeostasis, and

disruption of protective tissue barriers such as the BBB (Figure 3) [8,10,11]. Experimental animal models have shown that adult $PM_{2.5}$ and nPM pollution impact microglial function [39,40], leading to the release of proinflammatory cytokines and oxidative stress [22,39–42]. Further, $PM_{2.5}$ exposure has been directly linked to impaired myelin repair and aberrant myelination in an adult mouse model [43]. Recent animal and *in vitro* human studies have found that smaller particles can damage the BBB [21,22,44,45], potentially enabling the intrusion of both UFP-related pollutants and other potentially harmful substances. In turn, a leaky BBB may facilitate a further cascade of cytokines, oxidative stress, and metal accumulation in the brain [21,22,44]. Regarding the latter, particle pollution can include both trace elements and neurotoxic metals [9] and result in excess levels of metals in the brain [8]. Although many metals and trace elements are essential for optimal CNS function (e.g., iron, copper, and zinc), others are deemed non-essential toxins (e.g., Pb, cadmium, and mercury) [46]. Both trace amounts of non-essential metals and elevated amounts of essential metals can yield neurotoxic effects [47]. The regulation of metals in the CNS (i.e., metal homeostasis) includes selective transport across the BBB, intercommunication among astrocytes and neurons, and removal via the blood–cerebrospinal fluid barrier [48]. Therefore, exposure to air pollution can cause threefold disruption to brain metal homeostasis by transporting excess metals to the brain, enhancing BBB permeability, and/or impairing neuron–glia functioning. Downstream consequences of metal dyshomeostasis include neuronal death, oxidative stress, and mitochondrial dysfunction [49,50].

While much of this foundational literature is based on adult rodents, animal models of pollutant exposure during gestation and/or the early postnatal period (which is roughly equivalent to human childhood) support the growing concern about the potential neurotoxicant effects of air pollution on the developing brain. Gestational and early postnatal UFP exposure in mice, which is equivalent to the third trimester and shortly after birth in humans, has notable long-term consequences. These encompass structural brain changes, including to the hippocampus [51,52], corpus callosum [52,53], and ventricles (e.g., ventriculomegaly [53,54]), brain metal dyshomeostasis [55], changes in microglia and astrocyte phenotype [e.g., increases in glial fibrillary acidic protein (GFAP) and ionized calcium-binding adaptor molecule 1 (IBA-1) expression] [52,54,56,57], altered cytokine levels [54,58], and neurotransmitter imbalances (including disrupted excitation–inhibition balance) [54,56] (for reviews see [8,10]). Experiments in mice have shown that prenatal exposure can also cause accelerated oligodendrocyte precursor cell (OPC) differentiation in the corpus callosum in adolescence [59], which may further impact brain maturation given OPCs' contributions to myelination, BBB integrity, and the modulation of inflammatory responses in the brain [60]. Moreover, prolonged exposure in rodents, beginning with gestation and extending into the postnatal period that corresponds to adolescence, results in altered somatosensory cortical lamina organization [61], changes to cortical and hippocampus glial cells (e.g., increases in GFAP and IBA-1 expression) [62,63], altered hippocampal neurogenesis [51,64,65], and decreases in MRI-derived structural integrity within the anterior cingulate and hippocampus [66] (for reviews see [8,10]). Importantly, the direction and magnitude of the effects found tend to be age-, sex-, and brain-region-dependent [51,54,56,67]. Due to time-dependent shifts in neuronal–glial roles and hierarchical patterns of neuromaturation, the brain's developmental stage at the time of exposure is likely paramount to the anticipated region- and time-dependent effects. The studies to date examining exposure and/or neurotoxicity at multiple developmental windows support this notion [8]. For example, smaller corpus callosum volumes were noted in gestationally, but not postnatally, exposed mice, whereas mice exposed during both gestation and postnatal periods exhibited increases in microglia and astrocytes in the cortex, corpus callosum, and hippocampus [50]. Another study found both immediate and protracted onset of effects following early life exposure, including cytokine release and microglial changes in a sex-specific manner [54]. Therefore, air pollution may have
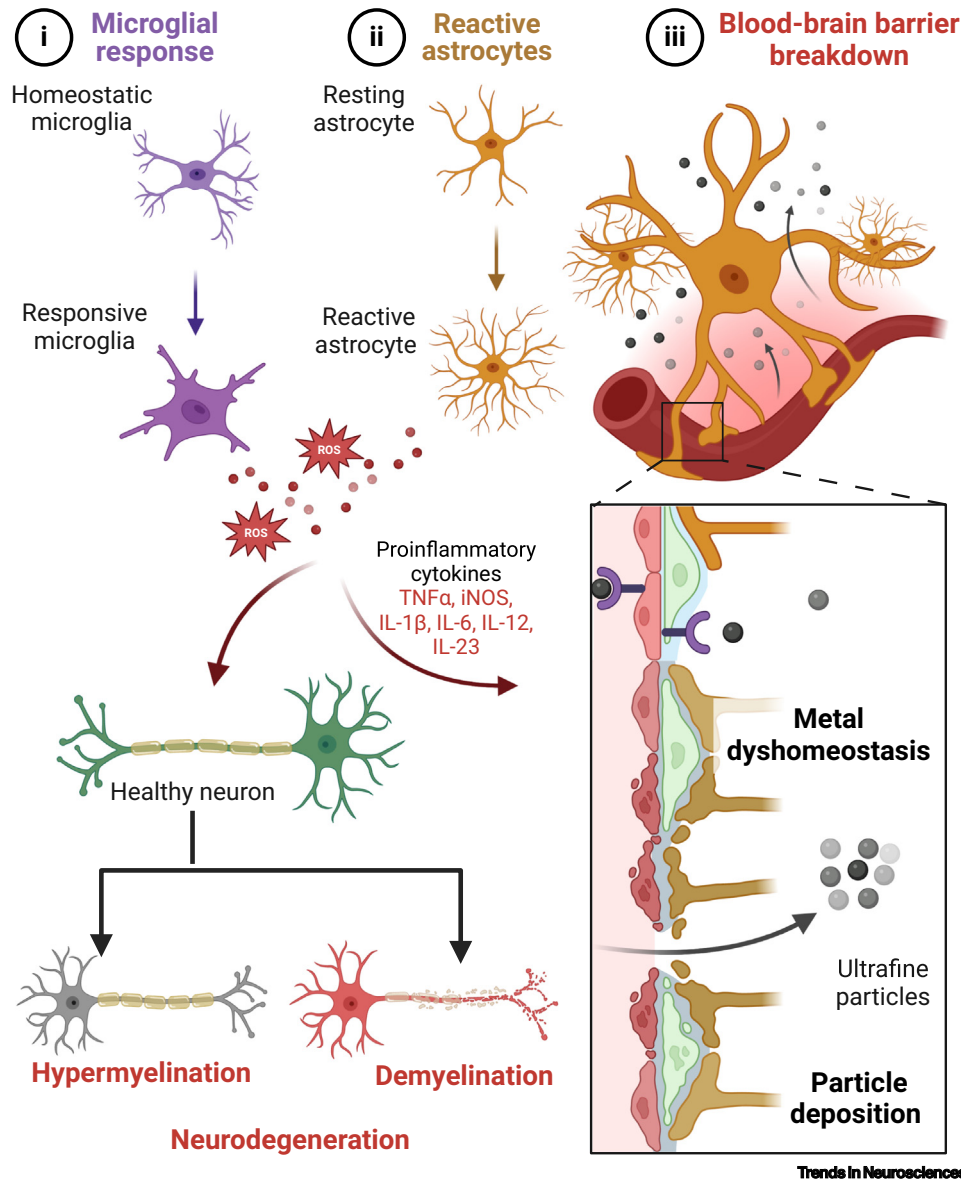
Figure 3. Actions of air pollution in the brain: impacts of peripheral inflammation and neurotoxicity. Based largely on animal exposure studies, the neurotoxic effects of air pollution exposure can manifest as alterations to glial cells that further facilitate damage to neurons and particle deposition in the brain. (i) Microglial responses to air pollution include phenotypic changes resulting in amoeboid morphologies (i.e., present a highly rounded morphology), the production of proinflammatory cytokines, and oxidative stress [39,40,49,53]. (ii) Another potential response to air pollution exposure comes from reactive astrocytes, which studies in rodents and *in vitro* models have shown can be induced from microglial responses and include proinflammatory phenotypes [49,148]. Reactive oxygen species (ROS) and proinflammatory cytokines, produced by microglial and astrocytic responses, may in turn result in hypermyelination [52,59], demyelination [42,43], or neurodegeneration of otherwise healthy cells [49,148]. (iii) Recent animal model studies and *in vitro* analyses of human-derived cells have also found that air pollution exposure can impair blood–brain barrier (BBB) function, including increased permeability [21,22,44,45]. A more permeable BBB may have additional downstream consequences, including, but not limited to, brain metal dyshomeostasis [49,50] and ultrafine particle (UFP) deposition [20,122]. Abbreviations: IL, interleukin; iNOS, inducible nitric oxide synthase; TNAα, tumor necrosis factor α. Figure created with BioRender.

immediate effects following exposure, and/or lasting effects on developmental process(es) that can persist into adulthood or even follow a protracted onset.

Altogether, air pollution exposure from conception through adolescence could disrupt microglia-driven synaptogenesis and later synaptic pruning functions, which, depending on the timing, could lead to inefficient and/or aberrant neural circuitry for sensorimotor, language, or higher-order cognitive brain circuits. Further impacts on both myelination and OPCs may disrupt white matter development, maintenance, and repair during childhood and adolescence, additionally compromising the development of efficient neural circuitry. Damage from prenatal air pollution exposure could impact BBB development *in utero*, while BBB damage from postnatal exposure may include astrocyte disruption and altered BBB permeability. Moreover, as each neural circuit reaches maturity, air pollution may also affect mature steady-state glial cells to produce more pathological profiles. These speculations require additional work to characterize time courses of air pollution neurotoxicity and vulnerability throughout development. Overall, the developmental inhalation toxicology literature provides strong evidence that air pollution exposure directly impacts cellular structure and function during brain development.

We now turn to the emerging evidence showing that everyday exposure to outdoor air pollution also affects the developing human brain as measured by MRI.

Human neuroimaging indicates that air pollution influences child and adolescent brain structure and function

MRI provides the opportunity to study the human brain *in vivo* across the lifespan [15], and MRI studies have been increasingly used to probe the neurodevelopmental consequences of ambient air pollution exposure (Table 2) [68,69]. Exposure to $PM_{2.5}$ and its components [e.g., polycyclic aromatic hydrocarbons (PAHs), copper, elemental carbon] as well as gaseous pollutants (e.g., ozone and nitrogen oxides) has been linked to various brain differences in children and adolescents, including brain macrostructure (i.e., cortical thickness, surface area, volume) [70–83], gray and white matter microstructure [70,77,84–86], cerebral blood flow [77], brain metabolites [77,87], and functional connectivity [79,88,89].

Structural imaging findings suggest that impacts of exposure are neuroanatomically localized, as air pollution is not related to global differences in brain structure, such as overall size or total gray matter volume [71–73,75–77]. Rather, exposure has been linked to differences in cortical thickness of frontal, parietal, cingulate, and temporal regions, as well as differences in basal ganglia, nucleus accumbens, and medial temporal lobe volumes [71–73,75–77,81,83]. Regional impacts of exposure may provide insight into downstream behavioral consequences. For example, frontal, parietal, and temporal regions exhibit protracted development into late adolescence and early adulthood [90], subserving the maturation of higher-order executive functions in humans. The basal ganglia and nucleus accumbens are integral to reward processing, motor planning, and the dopaminergic system [91]. Moving beyond shape and size, air pollution exposure has also been repeatedly linked to differences in microstructural tissue properties as measured by diffusion weighted imaging (DWI) in children and adolescents. This includes differences within key white matter tracts [70,77,78,84–86], suggesting less myelin, reduced fiber density, and/or less directional fiber coherence, as well as within subcortical gray matter brain regions [70,77] (Table 2). Building upon these efforts, our team has recently employed more advanced, histologically validated, biophysical modeling, known as restriction spectrum imaging (RSI) [92], to assess differences in intracellular water diffusion [86,93]. Our findings not only further support a link between $PM_{2.5}$ and differences in tissue microstructure during development, but also suggest that these differences stem from distinct increases in isotropic intracellular diffusion in the thalamus,

Table 2. Neuroimaging methods to study air pollution neurotoxicity in children and adolescents[a]

Imaging modality	MRI phenotypes linked to air pollution exposure	Proposed neurobiological mechanism(s)	MRI methods citation	In studies of air pollution exposure
Structural MRI (T1-weighted)	Cortical thickness, cortical, subcortical, and white matter volumes	Gray matter: synaptic pruning, cell density, nucleus volume White matter: axonal myelination	[149]	[70–83]
Diffusion-weighted imaging (DWI)	DTI: fractional anisotropy (FA), mean diffusivity (MD), apparent diffusion coefficient (ADC)	Gray matter: myelin density, myeloarchitectural, histological profile White matter: myelination/long-range projection axon development	[150]	Gray matter [70,77] White matter [77,84–86]
	RSI: restricted normalized isotropic (RNI), restricted normalized directional (RND)	Gray matter: cell bodies and neurites (neurogenesis, synaptic pruning, microglia activation) White matter: glial cells (microglia, astrocytes, oligodendrocytes) and microstructural integrity (myelination)	[92]	Gray matter [93] White matter [86]
BOLD functional MRI	Functional connectivity	Macroscale neural circuitry	[151]	[79,88,89]
	Task-based brain activation	Local field potential fluctuations coordinated with external stimulus	[152]	[79]
Arterial spin labeling/perfusion	Cerebral blood flow	Blood volume flow in brain tissue, tissue perfusion	[153]	[77]
MR spectroscopy	N-acetyl aspartate (NAA), myoinositol	Concentrations of brain metabolites	[154]	[77,79,87]

[a]Abbreviations: BOLD, blood oxygen-level-dependent; DTI, diffusion tensor imaging; RSI, restriction spectrum imaging.

brainstem, and accumbens [93], and in white matter pathways [86] at ages 9–10 years. These increases in intracellular diffusion may reflect more or larger spherical structures, such as cell bodies of neurons and supporting glial cells. These histologically validated microstructural measures offer a glimpse into the human parallels of some of the previously discussed cellular mechanisms from animal air pollution neurotoxicology studies, such as changes in microglia and astrocyte quantities and/or pathologically enlarged microglia.

Further, PM exposure has been linked to differences in metabolite levels and brain function. Proton MR spectroscopy has linked metabolite concentrations in the cingulate cortex to traffic-related air pollution exposure [77,87]. This includes increased myoinositol [87], a component of myelin and a metabolite found in glial cells responsible for regulation of osmotic pressure and cellular homeostasis, and N-acetylaspartate [77], which may be a marker of neuronal health. Furthermore, arterial spin labeling has linked prenatal $PM_{2.5}$ exposure to reduced regional cerebral blood flow, reflecting potential underlying differences in neurovascular processes and metabolic demands in frontal and visual cortices, as well as in white matter and subcortical regions [77]. Lastly, resting-state functional MRI has linked intrinsic brain activity differences to exposures in infancy, childhood, and early adolescence, revealing both greater within- and between-network resting-state functional connectivity [70,79,88,89]. This includes notable differences in the default mode network (DMN), which is especially active during passive rest and involved in internally focused thought processes [94]. Recent work from our team has showed that criterion ambient air pollutant exposure at ages 9–10 years is linked to distinct longitudinal changes in network connectivity over a 2-year follow-up period, suggesting potential long-term consequences of air pollution exposure on functional network maturation [89].

Most of these human neuroimaging studies leverage high-resolution spatiotemporal modeling to estimate air pollution exposure for the child based on a residential address. This method is widely used throughout the environmental epidemiology literature and provides a scalable approach to

estimating individual-level environmental exposure data for population-level studies focused on understanding neurodevelopmental impacts of air pollution. However, to date, the periods and durations of exposure examined vary between studies, making it difficult to draw definitive conclusions regarding the nature and degree of air pollution effects during specific developmental stages. Moving forward, lifetime estimates of exposure based on when and where individuals spend most of their time (e.g., home, school) are necessary to more fully characterize how air pollution impacts human brain development. Future studies implementing high-resolution spatiotemporal air pollution modeling with repeated brain scans can help uncover how neuroanatomically localized and timing-specific effects may map onto the cellular processes and neural systems that are most malleable to pollutant exposure during any given developmental window.

Air pollution, behavior, and population level impact

Although more research is needed, the neurotoxic effects of ambient air pollution discussed in the previous sections may reflect early biomarkers of risk for cognitive and overall health problems later in life. Beyond structural and functional differences noted in MRI, adverse neurobehavioral effects of ambient air pollution exposure have been observed during childhood and adolescence, including lower IQ [95–99] and impairments in cognitive function [100–103]. Accumulating evidence also suggests a link between air pollution exposure and mental health problems [104]. Prenatal and childhood air pollution exposure has been linked to subclinical symptoms of anxiety [105,106], depression [105,107], psychotic experiences [108], inattention, and other behavioral problems [109–112] in children and teens, as well as increased risk of autism spectrum disorder (ASD) [113] (for reviews see [114,115]). A few human studies report a direct link between exposure-related brain findings and concurrent behavioral deficits in children and adolescents [76–78,87]. Yet, we believe that many of the putative effects of air pollution may have a delayed onset. Even without any overt behavioral differences at the time of neuroimaging, the detectable brain differences following prenatal and childhood exposure may reflect early neural biomarkers of exposure-related risk that could manifest later in life. In fact, many toxicological studies of inhaled air pollution have demonstrated changes in depression [63,65,116–118], anxiety [58,66,117], and aggressive [119] behaviors as well as cognitive impairments [58,63,65,66,120] in adulthood following prenatal and postnatal PM exposure. This idea is also supported by recent findings that higher levels of air pollution during childhood and adolescence is not associated with concurrent behavioral differences, but rather predicts later onset of major depressive disorder [107] and other internalizing, externalizing, and thought disorder symptoms at age 18 years [121]. Building upon this lifespan perspective, it is also conceivable that developmental effects are emblematic of early risk factors for neurodegenerative diseases, in view of the differences in neurovascular properties, tau, and amyloid-β detected in postmortem brains from children and young adults from highly polluted urban cities [122,123]. Overlap between exposure-related neurotoxicity and neurodegenerative pathologies (e.g., metal dyshomeostasis, CNS inflammation, BBB damage) may suggest an increased risk for early neurodegeneration [124–126]. Linking exposure timing to regional brain differences and related behavioral changes may provide insight regarding implications of exposure for public health. Because urban air pollution exposure can be reduced by both behavioral changes and environmental regulations, we believe that longitudinal studies using non-invasive approaches (including MRI) have the potential to identify biomarker targets for early intervention.

Recent human MRI research, with relatively large sample sizes, suggests that everyday levels of air pollution exposure are linked to differences in the developing brain of youth. Of note, some of the existing child and adolescent brain differences identified are present at relatively low concentrations of pollutants, and recent evidence suggests that even low-level pollutant concentrations can be hazardous to human health more broadly [6]. It is feasible that, like other known

neurotoxicants, there truly may be no 'safe' level of exposure, especially when it comes to the developing brain [127]. Even if neurotoxicant effects are found to be modest, with 2.3 billion children and adolescents worldwide[ii], the impacts of long-term air pollution exposure on brain development could contribute to substantial differences in risk for cognitive, behavioral, and mental health outcomes at a population level. Together with its other well-known adverse health effects, the materializing neurotoxicological consequences of pollution on brain development further endorse the urgent call for cleaner air.

Concluding remarks and future perspectives

Along with animal models that provide clear evidence of air pollution neurotoxicity, human neuroimaging research increasingly suggests that air quality is linked to differences in the developing brain of children and adolescents. Additional research is necessary to fully characterize the impact of ambient air pollutants on the CNS during gestation, infancy, childhood, and adolescence (see Outstanding questions). Given the inherently dynamic and variable nature of brain maturation, additional studies are warranted that assess discrete periods and cumulative effects of exposure as they pertain to brain changes detected throughout development.

Emerging literature emphasizes that links between air pollution and health are not deterministic. Individual- and population-level characteristics beyond age contribute to susceptibility and vulnerability to air pollution's impacts on health [128], including neurotoxicity [129]. Animal studies have revealed sex differences in exposure-related dysregulation of neuroendocrine function, CNS inflammation [54], and metal dyshomeostasis [67], with potential moderating effects of stress and sex hormones in exposure-related neurotoxicity [130,131]. Similarly, recent human neuroimaging studies suggest that exposure-related differences vary by sex for several brain phenotypes [77,89], albeit not others [72,88]. Environmental injustice and structural racism also both contribute to individual differences in exposure to air pollution and ensuing neurotoxicity [132]. In the USA, the burden of exposure is not uniformly distributed; Black, Latino/Latina, and lower-income communities experience higher concentrations of pollution [133]. Individuals from underserved and lower-income communities may also face compounding effects of psychosocial stressors and air pollution to the detriment of children's health and wellbeing [129,134], including lasting epigenetic and endocrine effects [46,135]. Early adverse events and socioeconomic disadvantage have also been proposed to change the pace of neurodevelopment, including delay, acceleration, and/or initial delay followed by accelerated maturation, ultimately compounding the effects of air pollution to potentially promote risk for various poor health outcomes [83,136,137]. This highlights the importance of longitudinal studies with in-depth exposure estimates and brain outcomes in large, diverse participant samples that specifically include individuals from historically marginalized groups that face disproportionate exposures and historical exclusion from biomedical research [138,139].

Future research should determine whether the consequences of air pollution on brain structure and function noted herein are epiphenomena, or whether they may either mediate and/or moderate the associations seen between air quality and cognitive and psychological problems. Regardless, our hope is that this emerging topic within the field of environmental neuroscience will be of immediate and practical use for policy-makers charged with protecting public health. While additional research is needed on dosing effects, policy-makers should consider current research showing that low-level concentrations may still be harmful and strengthen regulatory standards accordingly, to ensure the human right to clean air and optimal brain health worldwide. Lastly, it should be noted that low-level exposure effects may be driven by pollutant composition rather than exposure to a single or even a few 'criteria' pollutants. Individuals are typically not exposed to a single pollutant, but rather to mixtures of pollutants emitted from various sources with geographic variability and differential health effects [9,140]. Future studies should pinpoint the most

Outstanding questions

How does the timing of exposure influence the impact of environmental toxicants on neurodevelopment? Future work should investigate the temporal dynamics of exposure occurring acutely, during discrete sensitive periods, and cumulatively over the lifespan to understand risk and resilience factors in how pollutants contribute to both neurodevelopmental and neurodegenerative disorders.

What are the cognitive, behavioral, and mental health consequences of air pollution exposure during sensitive periods of development? While researchers have begun to address this question, recent evidence is mixed, with several studies suggesting either a null or negative correlation between exposure and incidence of symptoms of psychopathology. Follow-up work should aim to identify potential confounders and further probe these counterintuitive findings.

How does the amount of exposure relate to downstream developmental and health effects? Many studies leverage linear models which assume that greater exposure is related to greater neurodevelopmental impacts, but there is a precedent for non-linear dose–response relationships in other realms of toxicology to suggest that this may not be the case. Together with findings that suggest counterintuitive protective effects of air pollution exposure, future work should characterize dose–response relationships, allowing for non-linearities.

How do neurodevelopmental consequences of exposure vary by pollutant type? Are some sources of outdoor air pollution more harmful than others? Outdoor air pollution comprises a complex mixture of gases and particles. Its composition depends on the sources of pollution, the distance pollutants have traveled, and interactions between pollutants. Thus, understanding the developmental and health effects of outdoor air pollution exposure, and translating that understanding into policy and behavior change, requires studies of both source-specific and mixture effects.

toxic component(s) of air pollution, and the sources thereof, to refine and strengthen air-quality guidelines in a global effort to safeguard brain health for all youth.

Declaration of interests

The authors declare no competing interests in relation to this work.

Resources

[i]www.who.int/health-topics/air-pollution#tab=tab_1

[ii]https://data.unicef.org/how-many/how-many-children-under-18-are-in-the-world/

[iii]www.epa.gov/criteria-air-pollutants/naaqs-table

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