Review

Biological Psychiatry

Environmental Toxicants and the Developing Brain

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ABSTRACT

Early life represents the most rapid and foundational period of brain development and a time of vulnerability to environmental insults. Evidence indicates that greater exposure to ubiquitous toxicants like fine particulate matter ($PM_{2.5}$), manganese, and many phthalates is associated with altered developmental, physical health, and mental health trajectories across the lifespan. Whereas animal models offer evidence of their mechanistic effects on neurological development, there is little research that evaluates how these environmental toxicants are associated with human neurodevelopment using neuroimaging measures in infant and pediatric populations. This review provides an overview of 3 environmental toxicants of interest in neurodevelopment that are prevalent worldwide in the air, soil, food, water, and/or products of everyday life: fine particulate matter ($PM_{2.5}$), manganese, and phthalates. We summarize mechanistic evidence from animal models for their roles in neurodevelopment, highlight prior research that has examined these toxicants with pediatric developmental and psychiatric outcomes, and provide a narrative review of the limited number of studies that have examined these toxicants using neuroimaging with pediatric populations. We conclude with a discussion of suggested directions that will move this field forward, including the incorporation of environmental toxicant assessment in large, longitudinal, multimodal neuroimaging studies; the use of multidimensional data analysis strategies; and the importance of studying the combined effects of environmental and psychosocial stressors and buffers on neurodevelopment. Collectively, these strategies will improve ecological validity and our understanding of how environmental toxicants affect long-term sequelae via alterations to brain structure and function.

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Dynamic changes in neurodevelopment take place across the lifespan, but the most prolific and foundational period arguably occurs from conception through early childhood (1). This period is also marked by a limited ability to metabolize and eliminate chemical exposures (2). According to decades of research testing the Developmental Origins of Health and Disease hypothesis, early life represents a sensitive window for environmental insults to modify neurological (as well as metabolic, endocrine, and immune) systems; however, these modifications often occur to the detriment of developmental outcomes and later health (3,4). With respect to the Developmental Origins of Health and Disease framework, "environmental insults" consists of insults in the social and physical environments, including environmental toxicants (5).

Environmental toxicants provide a broad categorization for substances in our immediate environment that have toxic effects on living organisms. These include, among others, many metals (e.g., lead, manganese), large and fine particulate matter, and endocrine-disrupting chemicals, such as phthalates and flame retardants. Epidemiological studies have linked greater exposure to many environmental toxicants with developmental deficits in children and adolescents and poorer physical and mental health outcomes in adults [e.g., (6–11)]. Evidence from animal models provides some mechanistic understanding of how such toxicants affect bodily systems, indicating the passage of many to the central nervous system [e.g., (12,13)], where they disrupt fundamental processes of brain development [e.g., (14–17)]. Despite their neurotoxic effects, these exposures are an inevitable part of the human experience because toxicants exist in the air, soil, food, water, and everyday commercial and consumer products (18–24). Furthermore, populations with lower socioeconomic status and systemic marginalization are at even greater risk for exposure to toxicants (25–28). For example, marginalized populations are more likely to live and work near outdoor air pollutant sources due to long-standing implications of racial segregation (29,30), leading to environmental inequality (28).

Although animal models have been vital in demonstrating the potential neurodevelopmental mechanisms of these toxicants, vast differences between human and animal brain development, physiology, and metabolic pathways among other methodological differences between human and animal studies limit the translation of neurodevelopmental findings across species (31). Environmental toxicant exposure during sensitive periods of brain development may profoundly alter developmental and health trajectories, yet research surrounding their mechanistic effects in infants and children using neuroimaging is understudied. It has been suggested that recent increases in pediatric neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD) and

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autism (32), are related to increasing environmental toxicant exposures (33). Neuroimaging research of early brain development related to these disorders has detected subtle differences in the structure of the brain that precede observable symptoms (34,35). Therefore, pediatric neuroimaging research could improve our understanding of early neurodevelopmental mechanisms underlying the effects of environmental toxicants on later developmental and psychiatric disorders. These data are important for informing environmental exposure thresholds, advisories for pregnant persons and families of young children, and early interventions focusing on both toxicant reduction and complementary strategies to offset neurodevelopmental impacts.

To demonstrate the gaps in neuroimaging studies of environmental toxicants, this narrative review examines the neurodevelopmental literature related to 3 different classes of environmental toxicants—fine particulate matter, manganese, and phthalates. In addition to their ubiquity and associations with child developmental outcomes, these examples were selected because 1) they represent exposures encountered across different sources (air, contaminated food/water, and products) (see Figure 1); 2) they represent exposures that range from being well-known toxicants to those that are suspected for their toxicity to health and development; and 3) we expect that most readers will find at least one of these toxicants relevant to their populations of interest. With a summary of the existing literature, we highlight research examining these toxicants with pediatric, developmental, and psychiatric outcomes and summarize the relevant and comparatively limited number of studies that have examined these toxicants using magnetic resonance imaging (MRI) in pediatric populations. We refer briefly to adult neuroimaging research when research has historically included older samples to contextualize the pediatric literature. Findings are summarized from pediatric neuroimaging studies that have examined exposure of each toxicant between pregnancy and adolescence (age 18 years). We encourage scientists to include environmental toxicants in pediatric neuroimaging research and suggest directions to move this field forward, including using multidimensional data analysis techniques and studying coexposure to multiple chemical and nonchemical toxicants.

FINE PARTICULATE MATTER ($PM_{2.5}$)

Although many airborne pollutants have been associated with decrements in child neurodevelopment [e.g., (36,37)], we focus

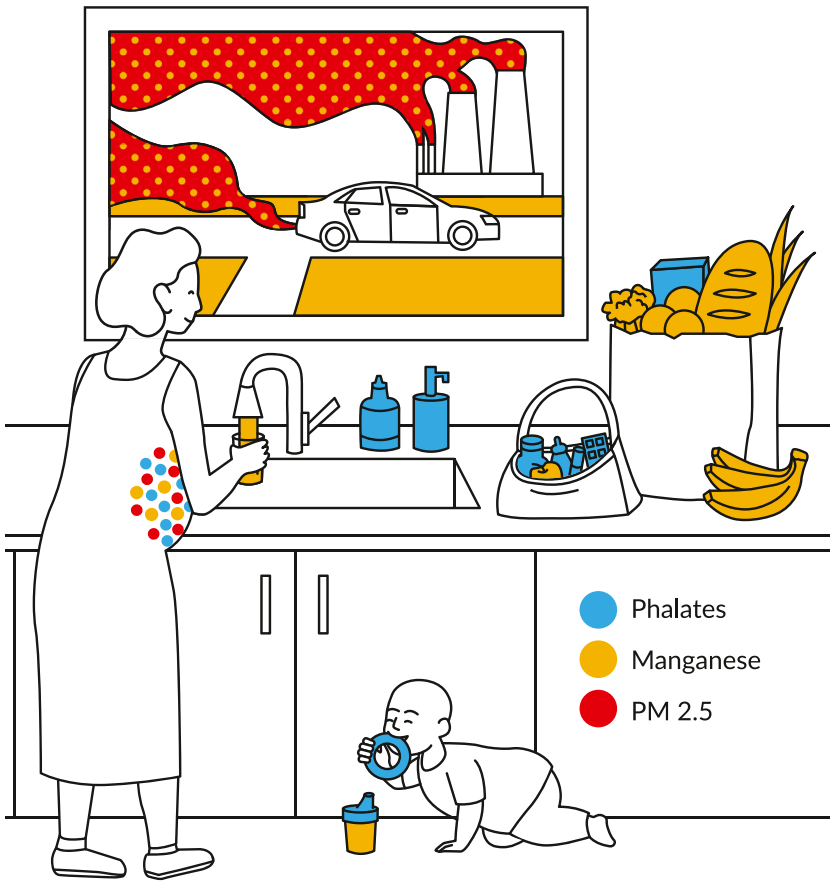

Figure 1. An illustrative and simplified example of potential sources of exposure to fine particulate matter ($PM_{2.5}$), manganese, and phthalates in pregnant persons and children. We note that manganese is both a trace element and a heavy metal; manganese is essential for biological functioning in appropriate doses, and adequate amounts of manganese for biological functioning are found naturally in foods. However, it is also possible for manganese to contaminate soil and water, thereby transferring to foods.

on fine particulate matter with a diameter ≤2.5 μm ($PM_{2.5}$). $PM_{2.5}$ exposure occurs through the combustion of diesel, gasoline, and other fossil fuels; tobacco smoke; wildfires; and the burning of agricultural waste (22–24). $PM_{2.5}$ are ubiquitous contaminants worldwide, but particularly in urban environments (23,38). Exposure is quantified using monitoring techniques and biological measures, including personal monitoring systems, land-use regression mapping, serum blood samples, and for prenatal exposure—placental adducts. Inhaled $PM_{2.5}$ reaches the central nervous system by migrating into the circulatory system and crossing the blood-brain barrier (13,39). $PM_{2.5}$ can also cross the placental barrier into the fetal compartment (40,41). Among other mechanistic pathways by which early-life exposure to $PM_{2.5}$ affects child neurodevelopment, research to date has implicated oxidative stress and neuroinflammation (spurred by respiratory tract inflammation) (13,42–44). In vitro studies demonstrate that oxidative stress caused by $PM_{2.5}$ induces mitochondrial damage (16,45), with downstream effects of oxidative stress and neuroinflammation including cellular damage, cell death, and changes to synaptic plasticity (13,44). More recent studies also suggest the involvement of epigenetic mechanisms (46).

Developmental and Psychiatric Outcomes of $PM_{2.5}$ Exposure

Increased exposure to air pollutants from pregnancy through later childhood is associated with reduced neurocognitive functioning as evidenced in developmental, academic, and behavioral domains (47,48). A recent systematic review of studies in preschool- and school-age children showed that prenatal exposure to several air pollutants, including $PM_{2.5}$, is robustly associated with later executive function and attentional deficits in 12 of 16 studies (11). Consistent evidence for learning and memory difficulties in childhood was also found in 7 of 12 studies that examined prenatal exposure (11). Other studies have shown that greater prenatal $PM_{2.5}$ exposure is associated with ADHD and autism (49,50). Postnatal traffic–related air pollution has also been repeatedly associated with decreased intelligence scores, child behavior challenges, and clinical conditions, including hyperactivity, externalizing behaviors, ADHD, and autism (36,51–53).

$PM_{2.5}$ and Pediatric Neuroimaging Studies

To date, fewer than 10 neuroimaging studies have examined prenatal $PM_{2.5}$ exposure, and even fewer have focused on pediatric exposure (see Table S1 for a summary of studies) (54–70). Results from these studies provide initial evidence that early-life $PM_{2.5}$ exposure interferes with the developing structure and function of the brain.

Abnormalities in white matter (WM) have been documented in several studies of prenatal $PM_{2.5}$ exposure. Specifically, higher prenatal exposure to $PM_{2.5}$ has been associated with increases in WM development—specifically, higher fractional anisotropy (a measure of WM integrity) and lower mean diffusivity (a measure of axonal packing) in numerous major WM tracts when children were imaged between 9 and 12 years of age (58). In a separate cohort, smaller WM volumes and reduced WM organization in the internal capsule and frontal lobe were documented in 6- to 14-year-old children who were exposed to $PM_{2.5}$ prenatally (61). Exposure severity also moderated the association of brain measures with children's scores for ADHD and anxiety symptom severity, social responsiveness, and intelligence (61).

The neurodevelopmental impact of prenatal exposure to traffic-related air pollution has been investigated in several subsets of the Generation R cohort (*N*s range from 736 to 3133) using various imaging modalities. Imaging results have shown reductions in child and preadolescent brain volumes (e.g., smaller corpus callosum) (57), alterations in WM microstructure (58), and reduced cortical thickness in the precuneus and rostral middle frontal regions that partially mediated associations with decreased inhibitory control (a component of executive function) (54). Whereas another study of the Generation R cohort did not find associations between prenatal $PM_{2.5}$ exposure and later network connectivity, exposure from birth to age 3 years was associated with higher brain network connectivity between the task-positive and task-negative networks in adolescence (56). Typically, these networks are anticorrelated; when the positive network is active during higher-order tasks, the negative network, associated with self-referential thoughts, is quiescent (71). Similarly, children (ages 8–12 years) exposed to higher levels of air pollution ($PM_{2.5}$ and nitrogen dioxide) had lower neural integration and segregation in networks for stimulus-driven processes and the default mode network (70). Findings from these studies are consistent with ADHD-related network abnormalities reported in other studies and align with the inattentive profile commonly reported in studies examining behavioral associations with $PM_{2.5}$ (72).

Childhood exposure to $PM_{2.5}$ is also associated with structural and functional brain alterations, even at levels of exposure that are below current U.S. Environmental Protection Agency regulatory standards (12 $\mu g/m^3$) (73). As researchers have begun to capitalize on neuroimaging data from the national ABCD (Adolescent Brain Cognitive Development) Study, findings suggest that current standards may need to be adjusted. Estimates of participants' annual mean $PM_{2.5}$ exposure were determined from home addresses and ensemble-based models (68,74). Despite relatively low annual mean $PM_{2.5}$ levels (7.63 ± 1.57 $\mu g/m^3$), exposure was associated with hemispheric and region-specific differences in gray matter (GM), which may reflect alterations in the concentration or volume of neuronal and glia cell bodies, neuropil, synapses, and capillaries. Results show both increases and decreases in GM volume, surface area, and cortical thickness (68). Imaging was conducted when participants were around 10 years of age—when cortical thickness begins to decrease due to normative synaptic pruning. Thus, whether observed differences are associated with accelerated and/or delayed maturational trajectories will remain undetermined until additional imaging data are released and examined longitudinally (68). Interestingly, no associations were observed between $PM_{2.5}$ exposure and cognition in this study. Another study of the ABCD cohort identified associations between annual levels of $PM_{2.5}$ exposure and WM alterations using restriction spectrum imaging (74). Results from this study show restricted isotropic intracellular diffusion in multiple WM tracts that are important for executive function and attention. These include the bilateral fornix and uncinate and the left cingulum and superior

longitudinal fasciculus, suggesting that higher exposure levels may lead to increases in cellular barriers in the WM and isotropic compartment (74) (see Figure 2).

Differential findings from pediatric neuroimaging studies examining $PM_{2.5}$ could be attributed to multiple factors (e.g., imaging modality; exposure timing, level, and chronicity) that will need to be addressed with more systemic research. Whereas the developmental literature indicates that consequences are potentially greater for individuals who are exposed prenatally, additional neuroimaging research is needed to specify the ways in which exposure timing impacts the developing brain. Still, common patterns have emerged that are consistent with developmental and clinical findings, including alterations in brain regions that support executive functions, attention, and emotion regulation or overlap with aberrant patterns observed in clinical conditions such as ADHD (54,61,72,74). Although disruptions in WM integrity and volume have been reported most often (55,58,59,61,65–67,74), multiple studies have identified lower segregation of functional neural networks (56,70) that are important for regulating attention and inhibitory control. Volumetric anomalies in the cerebellum and subcortical structures, including the thalamus and basal ganglia, were also common among several studies (57,59,61–63,68). Only one study found sex-specific effects (61), although few studies examined these relations. Similarly, few studies have examined the neurodevelopmental impacts

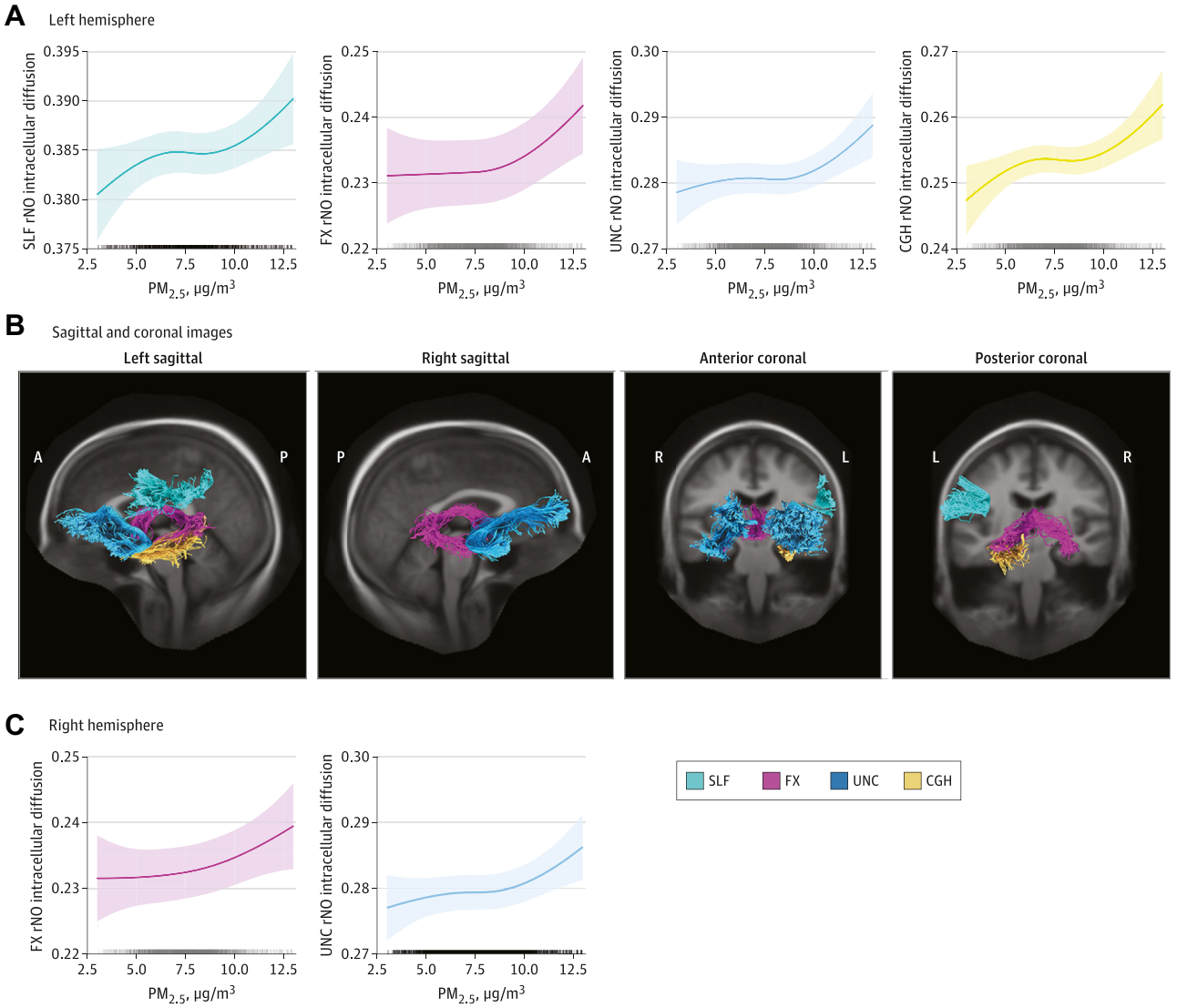

Figure 2. Associations between particulate matter ($PM_{2.5}$) and restricted isotropic diffusion. Selected from Burnor *et al.* (74). Annual mean $PM_{2.5}$ exposure is associated with increases in restricted isotropic intracellular diffusion (rNO) microarchitecture in specific white matter tracts of the left and right hemispheres. Spline plots reflect model-predicted values of rNO associated with annual mean $PM_{2.5}$ exposure, with all other model covariates held constant **(A, C)**. Sagittal and coronal images of relevant white matter tracks are provided for reference and colored to match spline plots **(B)**. A, anterior; CHG, cingulum hippocampal portion; FX, fornix; L, left hemisphere; P, posterior; R, right hemisphere; SLF, superior longitudinal fasciculus; UNC, uncinate fasciculus.

of exposure using task-based functional MRI (fMRI); such studies would be informative. Currently, no study has investigated $PM_{2.5}$ exposure in relation to the brain before 6 years of age.

MANGANESE

Manganese is both a trace element and a heavy metal, and it is essential for brain development in appropriate doses; however, overexposure is toxic to health and development (75). Humans acquire adequate amounts of manganese from nutritional sources, with toxicity tending to occur through contaminated air, water, and soil/foods or through occupational hazards including metal processing (75). During in utero exposure, manganese can cross the placental barrier into the fetal compartment (76), and manganese passes through the blood-brain barrier (12,77). Manganese accumulates in both GM (neurons and astrocytes) and WM (oligodendrocytes) (14,75) and causes dopaminergic dysfunction (e.g., inhibiting dopamine uptake) (78). Manganese may also increase oxidative stress, which may indirectly reduce neurogenesis and neuronal connectivity and diminish long-term potentiation (42,79,80).

Developmental and Psychiatric Outcomes of Manganese Toxicity

Research on the effects of early-life manganese toxicity has often observed negative associations with cognition in young children who were exposed in utero (7,81,82) and with cognitive, motor, and behavioral outcomes after childhood exposure (6,7). A 2015 review reported that 12 of 14 studies of early manganese toxicity found negative associations with prospective and concurrent cognitive outcomes, particularly with intelligence, and in the domains of memory and language (7). Prospective studies of early manganese exposure have demonstrated U-shaped associations with child cognitive outcomes that reflect the importance of appropriate manganese doses for biological functioning (83,84). Associations between early-life manganese exposure and clinical developmental outcomes, including ADHD and other behavioral outcomes, have been less consistent (7); whereas some studies have found increased risks of ADHD and internalizing and externalizing problems among children with higher manganese exposure, others have not (85–87). Such differences may be a function of study samples, timing, or duration of exposure and/or co-exposures. For example, there is evidence that lead moderates the effects of manganese on developmental outcomes (82).

Manganese and Pediatric Neuroimaging Studies

Despite evidence of the damaging effects of early-life manganese toxicity on child developmental outcomes, there is a dearth of research examining pediatric neurodevelopment using imaging (see Table S2 for a summary of studies) (88–93). Imaging studies typically leverage samples of occupationally exposed adults and control participants [e.g., (94–96)]. These studies provide context for the scant pediatric neuroimaging literature, with results that implicate the basal ganglia and cerebellum—key neural substrates involved in cognitive and motor functioning (7,94,95)—as targets of manganese toxicity (94,95).

The few studies that have explored early manganese toxicity in relation to child or adolescent neurodevelopment provide evidence for associations with altered patterns of intrinsic functional connectivity (iFC)—the strength of signaling between functionally coupled brain regions. Specifically, a study of prenatal blood manganese and iFC in middle childhood demonstrated reduced connectivity in the anterior cingulate cortex and orbitofrontal cortex; the inferior frontal gyrus, insula, and amygdala; and between the right globus pallidus and dorsal anterior cingulate cortex (89). These cortical and subcortical structures are implicated in the cognitive, behavioral, and motor deficits associated with manganese toxicity (89,97), with the authors specifically postulating that these functional networks may be linked to internalizing and externalizing disorders (87,89,98). Deciduous teeth have also been used to evaluate prenatal, postnatal, and/or early childhood manganese exposure with iFC in brain regions implicated in cognitive and motor deficits in adolescents (88,90). In a sample of adolescents (ages 12–18), manganese exposure during the first year of life (but not in utero) was positively associated with iFC between the bilateral middle frontal gyrus and left medial prefrontal cortex but negatively associated with iFC between the right putamen and left pre- and postcentral gyrus (88). This observed pattern of connectivity has been associated with reduced executive function abilities (working memory) and motor impairment (88,99,100). In a larger sample followed until later adolescence (ages 15–23), sex-specific effects were observed (90). Specifically, prenatal manganese was associated with decreased iFC in the left caudate and left occipital pole and in the left putamen and left occipital fusiform gyrus, but it was associated with increased iFC in the left putamen and middle frontal gyrus and in the middle frontal gyrus and right occipital pole in males; however, the opposite pattern was observed in females (90). Differential patterns of effects were observed for postnatal and childhood manganese exposure. The connectivity of several affected networks is associated with cognitive skills like language in young children (90,101). Manganese exposure may interfere with axonal development and early myelination, leading to observed neurodevelopment alterations. Together, the results from these studies highlight the potential for unique effects of metal toxicity on neural network connectivity depending on the timing of exposure and the importance of considering differential effects by sex (90).

Analyses of childhood manganese exposure on neurodevelopment have also identified components of the basal ganglia as targets of manganese toxicity. In a small sample of school-age children exposed to manganese-contaminated drinking water versus control children, manganese-exposed children demonstrated enlargement of the anterior and posterior ends of the putamen, increases in broad surface area of the putamen, and reduced signal intensity of the globus pallidus (92,93). The anterior left putamen was also correlated with reduced motor performance (93). Because the basal ganglia is highly involved in the coordination of cognitive and motor functions, these results are again consistent with the literature demonstrating the detrimental effects of childhood manganese toxicity on cognitive and motor development (7,93).

Studies of prenatal and childhood exposures provide support for the idea that manganese toxicity affects the structure

and connectivity of the basal ganglia (89,90,102)—substrates of which are highly involved in cognitive and motor functioning. Additional alterations in functional connectivity between areas of the prefrontal cortex and the insula and amygdala are also consistent with the developmental evidence that manganese toxicity affects child intelligence and behavioral problems (6,7,82,88,89). Moreover, there is compelling preliminary evidence for differential effects of manganese on functional connectivity between areas underlying cognitive and motor development based on exposure timing—including narrow windows between pregnancy and infancy (88–90). Only one study has examined moderations by sex, finding disparate patterns of functional connectivity by sex and exposure period (90) and, despite evidence for moderating effects in the developmental literature (82), no studies have examined the joint effects of manganese and lead exposure.

PHTHALATES

Phthalates are nonpersistent organic pollutants that make plastic flexible and durable or are found in cosmetic products (103,104). Common exposure routes include dermal absorption (e.g., contact with building materials, medical supplies, food packaging, and personal care products) (18,19) and the ingestion of contaminated foods (104,105). These chemicals are ubiquitous; for example, the 1999–2000 U.S. National Health and Nutrition Examination Survey indicated that all people had a detectable level of urinary di(2-ethylhexyl) phthalate (DEHP; a parent compound of phthalate metabolites) (106). Exposure to phthalates is often quantified through urine, blood, or personal monitoring methods. In analyses, phthalate metabolites are examined as composite measures according to their metabolic weight or as individual exposures. Phthalates are considered endocrine-disrupting chemicals due to their ability to affect hormone function (e.g., via hormone mimicry, synthesis disruption) (15,107,108), such as maternal and fetal sex hormones (by reducing testosterone synthesis) (18,109–111) and thyroid hormone in children and pregnant women (112,113). Both hormones are critical for healthy brain development (108,114,115)—gonadal hormones aid in regulating neuronal development (116), and thyroid hormone is implicated in neurogenesis, myelination, and neuronal and glial differentiation (117,118). Among other mechanisms, phthalate exposure is associated with increased oxidative stress (119–121), which has been implicated as a mechanism underlying associations with adverse birth outcomes (122).

Phthalates and Developmental and Psychiatric Outcomes

Systematic reviews generally indicate that early-life exposure to phthalates is associated with poorer cognitive and behavioral outcomes in childhood (8,9) and, at a minimum, sexually dimorphic effects as a function of specific phthalate metabolites (10). For example, prenatal exposure to low-molecular-weight phthalates (found in personal care products, medication coatings) has been associated with poorer child executive function and behavior, including more aggression, conduct problems, and depression and poorer attention and emotional control, with stratified analyses indicating that some associations are sex specific (123). In a study of individual metabolites, mono-*n*-butyl phthalate (MnBP) was associated with emotionally reactive, withdrawn, and internalizing behavior in boys. In girls, MnBP was associated with poorer mental development scores, and MBzP (monobenzyl phthalate) was associated with more anxious/depressed symptoms and internalizing behavior (124). Studies of early-life exposure to DEHP have also reported negative associations with cognitive development scores in early childhood (125).

Phthalates and Pediatric Neuroimaging Studies

Although there is growing interest in the role of phthalate exposure in developmental outcomes, there are few human neuroimaging research studies (see Table S3 for a summary of studies) (126–129). These studies have investigated the role of prenatal exposure on child and adolescent GM volumes (127), spontaneous brain activity, and local homogeneity of the resting-state fMRI signal (128) and WM integrity (126,127) in relation to developmental outcomes. For instance, one study investigating whether WM integrity (fractional anisotropy and mean diffusivity) mediated associations between maternal prenatal high-molecular-weight phthalates (which act as plasticizers) and child behavior problems found no direct effects on internalizing or externalizing behavior, although there was evidence for indirect effects (126). Specifically, high-molecular-weight phthalate concentration was positively associated with mean diffusivity of the right inferior fronto-occipital fasciculus, which was associated with internalizing and externalizing behaviors in preschool-age children (126). Similarly, increased mean diffusivity of the right pyramidal fibers mediated the associations between high-molecular-weight phthalate concentration and child internalizing problems (126). Altered WM integrity of these specific tracts has been shown, in this and other studies, to underlie cognitive, speech, and motor skills and related child behavior problems (126,130–134).

Two studies of the effects of prenatal phthalate exposure on adolescent (ages 13–16) neurodevelopment evaluated associations with fluctuations in spontaneous brain activity and homogeneity of the resting-state fMRI signal and GM and WM volumes, among other measures (127). Higher prenatal exposure to monobutyl phthalate (MBP) was associated with lower spontaneous brain activity in the superior frontal gyrus and middle frontal gyrus and positively associated with local homogeneity of the resting-state fMRI signal in the left middle temporal gyrus and left inferior temporal gyrus (128). Other studies have demonstrated positive associations between MBP and delinquent and aggressive behavior (135) and negative associations between activation in brain regions associated with aggression (128,136). Higher prenatal exposure to MBzP was associated with lower spontaneous brain activity in the left and right anterior cingulum gyrus and lower homogeneity of the resting-state fMRI signal in the right insula in adolescent girls (128). This metabolite has been associated with increased anxiety and depression in girls (124). These and other metabolites were also negatively associated with cingulate (MBP and MBzP) and cerebellum [MBP, MBzP, DEHP, and MEOHP (mono(2-ethylhexyl) phthalate)] volumes (127). Alterations in cortical structures and their functional connectivity may explain the increased

risk for ADHD, its symptoms, and other cognitive and learning deficits in children with higher exposure to phthalates (123,124,137).

Although phthalate exposures have been increasingly associated with child development, neuroimaging research in this area is still emerging. The few existing studies offer evidence that prenatal phthalate exposure predicts alterations in functional connectivity, WM integrity, and regional brain volumes in children and adolescents (126–128) and that childhood/adolescent exposure predicts concurrent temporal cortical thickness (126–129). Although phthalates are known endocrine disrupters, only 2 (of 4) studies examined moderations by sex, with 1 study identifying sex-specific functional effects (128). Studies examining neuroimaging and developmental/psychiatric measures have demonstrated that alterations to brain structure and function may mediate the effects of phthalate exposure on child outcomes including behavioral problems (126,129).

SUMMARY OF ENVIRONMENTAL TOXICANTS AND PEDIATRIC NEUROIMAGING

Despite the evidence that $PM_{2.5}$, manganese, and phthalates affect child developmental and psychiatric outcomes (including in early childhood), we identified few studies that examined these toxicants in pediatric populations using neuroimaging methods (see Table 1). As expected, the number of studies using neuroimaging for each toxicant tended to coincide with the history of that toxicant in the developmental literature. For example, we found only 4 studies that examined early phthalate exposure and pediatric neuroimaging outcomes, and the literature into the developmental implications of phthalate exposure is similarly emerging. The lack of research makes it difficult to synthesize the structural and functional neurological implications of each toxicant because few studies have examined overlapping outcomes. With increased study (and replication) in pediatric populations, scientists will be able to rigorously identify the neurological effects of toxicants and examine differences in outcomes by levels and chronicity of exposure, exposure routes, effect modifiers (e.g., sex), and co-exposures. Moreover, almost no neuroimaging studies have examined effects in infant and early childhood populations (i.e., children younger than 6 years)—arguably the most sensitive and dynamic period of brain development during the lifespan. This period also represents a time when the body has a limited capacity to metabolize such toxicants. Therefore, we call for additional large-scale, longitudinal, and multimodal imaging research (to include functional measures not discussed here such as electroencephalography) to better understand the early and long-term effects of early toxicant exposure on the developing human brain. In doing so, we offer considerations for scientists as they embark in this area of study.

FUTURE DIRECTIONS

Leverage Ongoing Pediatric Neuroimaging Studies

To address the gap in pediatric neuroimaging research, existing public environmental contaminant data (e.g., from geographic information systems and land-use regression models) can be combined with existing multisite, multimodal imaging data to better understand the implications of early-life toxicant exposure. Examples include the dHCP (Developing Human Connectome Project), the BCP (Baby Connectome Project), and the HBCD (HEALthy Brain and Child Development) Study. As data from these federally funded studies become available, we recommend that scientists leverage these data to investigate the impact of environmental toxicants on early brain development, including combining measures of brain structure and function. It may also be possible for these ongoing studies to measure environmental toxicant exposure using biomarkers or personal monitoring devices (e.g., urine, silicone wristbands). Other longitudinal, multimodal neuroimaging studies are underway that are measuring toxicant exposure and developmental and/or behavioral outcomes [e.g., (138–140)]. Combining structural and functional neuroimaging methods with developmental, behavioral, and health outcomes research will allow us to form a more comprehensive understanding of the effects of environmental toxicant exposure during early stages of development and their long-term developmental sequelae. We also encourage researchers to use these larger studies to examine sex-specific effects of environmental toxicants because this is another gap in this area of research.

Leverage Multidimensional/High-Dimensional Data Analysis

Individual environmental toxicants across (e.g., metals with air pollutants) and within (e.g., phthalate metabolites) classes are often moderately to highly correlated [e.g., (105,141)]. However, the studies reviewed herein did not consider the interacting effects of chemicals across classes. To improve the ecological validity of analytic models, environmental science is increasingly leveraging multidimensional and high-dimensional data analysis techniques such as Bayesian kernal machine regression, weighted quintile sum regression, K-means clustering, and LASSO regression to consider how exposure to co-occurring toxicants is jointly associated with developmental and health outcomes (142). Mixture modeling techniques like latent profile analysis can also identify naturally observed subpopulations with similar exposure profiles. These quantitative methods will provide a better understanding of how common mixtures of toxicants are associated with neurodevelopment.

Consider the Physical and Social Environments Together

Environmental toxicants and psychosocial stressors also tend to co-occur, especially in socioeconomically disadvantaged or minoritized populations (25–28), because social vulnerability often predisposes people to chemical exposures. Thus, studying stressors from social and physical levels of the environment is important for understanding the unique effects of each, ruling out potential confounds, and is more ecologically valid than studying stressors in isolation (143). Indeed, emerging research has demonstrated the moderating effects of environmental toxicants and psychosocial stressors on indices of neurodevelopment [e.g., (24,86,109)]. This research may help to

Table 1. Summary of Neuroimaging Studies Investigating Pediatric Brain Development and Toxicant Exposures

Number of Pediatric Studies by Toxicant	Country	Study Sample: Sample Size	Study Sample: Chemical Exposure and Measurement	Study Sample: Age at Exposure	Study Sample: Age at Neuroimaging	Imaging Modality	Developmental/ Psychiatric Measures	Neuroimaging Main Effects	Neuroimaging Sex-Specific Effects
$PM_{2.5}$									
18 Pediatric Studies Reviewed	North America: 7/18 studies Europe: 8/18 studies Mexico: 3/18 studies	*N*s ranged from 30 to 10,343 Median *N* = 214 Mean *N* = 1593	Residential: 14/18 studies School: 2/18 studies Personal monitoring: 3/18 studies	Prenatal/infant exposures: 5/18 studies Prenatal or infancy and childhood: 8/18 studies Childhood/ adolescent exposures: 5/18 studies	Infancy and early childhood (0–5 y): 0/18 Middle-late childhood (6–12 y): 17/18 studies Adolescence (13–19 y): 1/18 studies	sMRI assessing volumes, cortical thickness or surface area: 13/18 studies sMRI assessing signal intensity: 1/18 studies DWI/DTI assessing white matter microstructure: 4/18 studies rs-fMRI assessing functional connectivity: 2/18 studies fMRI assessing task-based response: 1/18 studies MRS assessing metabolites: 3/18 studies	Cognitive developmental outcomes: 10/18 studies Behavioral or clinical outcomes: 7/18 studies Socioemotional outcomes: 1/18 studies Physical health outcomes: 1/18 studies No developmental or psychiatric outcomes: 6/18 studies	Observation of main effects for studies using sMRI to assess volumes, cortical thickness, or surface area: 11/12 studies. Observation of main effects for studies using sMRI to assess signal intensity: 1/1 study Observation of main effects for studies using DWI/DTI to assess white matter microstructure: 3/4 studies Observation of main effects for studies using rs-fMRI to assess functional connectivity: 2/2 studies Observation of main effects for studies using fMRI to assess task-based response: 0/1 study Observation of main effects for studies using MRS to assess metabolites: 2/3 studies Observation of main effects for studies using ASL to assess blood flow: 1/1 study	Examination of sex-specific effects: 5/18 studies No examination of sex-specific effects: 13/18 studies Observation of sex-specific effects: 1/18 studies
Manganese									
6 Pediatric Studies Reviewed	North America: 3/6 studies Europe: 3/6 studies	*N*s ranged from 14 to 71 Median *N* = 19 Mean *N* = 27	Residential locations/ evidence of contamination: 3/6 studies Blood: 1/6 studies Teeth: 2/6 studies	Prenatal/infant exposures: 4/6 studies Childhood/ adolescent exposures: 4/6 studies	Infancy and early childhood (0–5 y): 0/6 studies Middle-late childhood (6–11 y): 3/6 studies Adolescence (10–19 y): 5/6 studies	sMRI assessing volumes or surface area: 2/6 studies sMRI assessing signal intensity: 1/6 studies rs-fMRI assessing iFC: 4/6 studies rs-fMRI assessing correlational analyses: 1/6 studies	Cognitive developmental outcomes: 1/6 studies Motor developmental outcomes: 2/6 studies Physical health outcomes: 1/6 studies No developmental or psychiatric outcomes: 3/6 studies	Observation of main effects for studies using sMRI to assess volumes or surface area: 1/2 studies Observation of main effects for studies using sMRI to assess signal intensity: 1/1 study Observation of main effects for studies using rs-fMRI to assess iFC: 3/4 studies Observation of main effects for studies using rs-fMRI for correlational analyses: 0/1 study	Examination of sex-specific effects: 1/6 studies No examination of sex-specific effects: 5/6 studies Observation of sex-specific effects: 1/1 study

Table 1. Continued

Number of Pediatric Studies by Toxicant	Study Sample						Neuroimaging Main Effects	Neuroimaging Sex-Specific Effects
	Country	Sample Size	Chemical Exposure and Measurement	Age at Exposure	Age at Neuroimaging	Imaging Modality	Developmental/ Psychiatric Measures	
Phthalates								
4 Pediatric Studies Reviewed	North America: 1/4 studies Asia: 3/4 studies	*Ns* ranged from 49 to 115 Median $N = 68$ Mean $N = 75$	Urinary phthalates: 4/4 studies Specific phthalate metabolites or parent compound (e.g., MBP, DEHP): 3/4 studies Phthalate composite: 1/4 studies	Prenatal exposures: 3/4 studies Childhood/ adolescent exposures: 1/4 studies	Infancy and early childhood (0–5 y): 1/4 studies Middle-late childhood (6–11 y): 2/4 studies Adolescence (10–19 y): 3/4 studies	sMRI assessing volumes, surface area, or cortical thickness: 2/4 studies DTI: 1/4 studies rs-fMRI assessing fALFF: 1/ 4 studies	Cognitive developmental outcomes: 1/4 studies Socioemotional outcomes: 1/4 studies No developmental or psychiatric outcomes: 2/4 studies	Observation of main effects for studies using sMRI to assess volumes, surface area, or thickness: 2/2 studies Observation of main effects for studies using DTI: 1/1 study Observation of main effects for studies using rs-fMRI to assess fALFF: 1/1 study	Examination of sex-specific effects: 2/4 studies No examination of sex-specific effects: 2/4 studies Observation of sex-specific effects: 1/2 studies

The table provides a summary of study characteristics and results from the pediatric neuroimaging studies reviewed in this article. See also Tables S1–S3 and their cited references for more details.

ASL, arterial spin labeling; DEHP, di(2-ethyl-hexyl) phthalate; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; fALFF, fractional amplitude of low-frequency fluctuation; fMRI, functional magnetic resonance imaging; iFC, intrinsic functional connectivity; MBP, mono-*n*-butyl phthalate; MRS, magnetic resonance spectroscopy; $PM_{2.5}$, fine particulate matter; rs-fMRI, resting-state fMRI; sMRI, structural MRI.

more accurately identify subpopulations at risk (144) and create better-informed interventions to reduce developmental decrements (145). However, in our review we identified only one study that examined moderations by social stressors (60). Similarly, unmeasured confounding via protective social factors (e.g., caregiving, nutrition) may also explain heterogeneity in the effects of environmental toxicants on neurological and developmental outcomes. Yet, previous research has rarely considered how positive social and behavioral factors may buffer the effects of environmental toxicants on neurodevelopment (146,147). Considering the ubiquity of many toxicants, it is advantageous to evaluate strategies to offset the effects of these stressors on neurodevelopment.

CONCLUSIONS

This review highlights 3 ubiquitous and understudied environmental toxicants—$PM_{2.5}$, manganese, and phthalates—that are encountered across various sources. Whereas these toxicants have documented detrimental effects on development and health, the limited number of studies evaluating their specific neurodevelopmental effects using neuroimaging indicates that much of this research is still preliminary. Additional research is needed to investigate potential consequences of exposure to these environmental toxicants and many others (e.g., flame retardants, per- and polyfluorinated substances, other toxic metals) in relation to brain structure and function during the sensitive period of early neurodevelopment in humans. This information is also important for 1) detecting neurodevelopmental differences prior to observable symptoms of disorders, 2) designing interventions aimed at remediating the effects of exposures, and 3) informing federal exposure standards. We encourage scientists to consider these and other toxicants in their models of early risk, work collaboratively with environmental scientists, and create innovative research strategies that promote safe and healthy environments for the developing brain.

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