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Toxicant exposure and the developing brain: A systematic review of the structural and functional MRI literature

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Abstract

Youth worldwide are regularly exposed to pollutants and chemicals (i.e., toxicants) that may interfere with healthy brain development, and a surge in MRI research has begun to characterize the neurobiological consequences of these exposures. Here, a systematic review following PRISMA guidelines was conducted on developmental MRI studies of toxicants with known or suspected neurobiological impact. Associations were reviewed for 9 toxicant classes, including metals, air pollution, and flame retardants. Of 1,264 identified studies, 46 met inclusion criteria. Qualitative synthesis revealed that most studies: (1) investigated air pollutants or metals, (2) assessed exposures prenatally, (3) assessed the brain in late middle childhood, (4) took place in North America or Western Europe, (5) drew samples from existing cohort studies, and (6) have been published since 2017. Given substantial heterogeneity in MRI measures, toxicant measures, and age groups assessed, more research is needed on all toxicants reviewed here. Future studies should also include larger samples, employ personal exposure monitoring, study independent samples in diverse world regions, and assess toxicant mixtures.

Keywords

MRI; brain structure; brain function; toxicant exposure; pollution; development; childhood; adolescence

1. Introduction

Despite increasing concern for the protection of children from chemicals and pollutants with the potential to harm the central nervous system (i.e., toxicants) (Landrigan et al., 2018), toxicant exposure remains widespread in our environment (Hoffman et al., 2018). Toxic chemicals such as heavy metals, pesticides, solvents, plasticizers, and flame retardants can now be found in the air, water, and soil and, increasingly, in food, furniture, clothing,

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and personal care products. Consequently, national biomonitoring programs routinely detect most major toxicant classes in the blood and urine of American children (Hendryx & Luo, 2018). The presence of these chemicals in children's bodies is concerning, as occupational exposure studies demonstrate a clear link between toxic chemicals and disrupted neurological function (Flynn & Susi, 2009; Lucchini et al., 2009; Van Maele-Fabry et al., 2012).

Although children typically do not have occupational exposures, they are at even greater risk of toxicant harm than adults due to their physiology and behavior. Children have fewer biological defenses against toxicant exposure than adults (e.g., fewer detoxifying enzymes; (Cole et al., 2003)) and their brains are still-developing (Mills et al., 2016), meaning that they may experience lasting disruptions to brain development, with potential lifelong consequences for personality, cognitive ability, mental health, and social mobility (Reuben et al., 2017, 2019). Children also consume more food, water, and air per unit of body weight than adults (Environmental Protection Agency, 2002), and thus absorb more of a toxic substance than adults when exposed. Children's behavior also causes them to be at higher exposure: children have greater hand-to-mouth activity (Xue et al., 2007), are closer to the ground where toxicants may settle (Stapleton et al., 2009), and are more likely to eat foods containing higher levels of toxicants (e.g., fruit, juice) (Eskenazi et al., 2007).

While researchers have known for decades that certain toxicants (e.g., lead) have negative behavioral and cognitive effects, research exploring the effects of toxicant exposure on the developing human brain was rare until approximately twenty years ago. At that time, developmental neuroscientists and environmental health researchers began using non-invasive neuroimaging techniques to assess associations between toxicant exposure and developing brain structure and function *in vivo*. Since then, research in this topic has steadily increased, with most research examining neurobiological effects of individual—rather than cumulative—exposures. This research has begun to answer important questions about which toxic chemicals are of greatest concern for brain development, what brain structures and functions are affected, and how the course of brain development may be impacted.

Thus, the time is right to build on previous work to create the first systematic review following PRISMA guidelines on developmental MRI studies of all toxicants with known or suspected neurobiological impact. This will provide key information about the current state of the MRI literature by indicating what toxicants, age groups, locations, and measures are most often studied and where additional research is needed to fill existing knowledge gaps. Second, by reviewing the effects of more than one toxicant class at once, the current review will provide a point of departure for identifying toxicants with similar effects on the developing brain. Understanding which toxicants may have similar neurobiological effects is critical for identifying candidates for simultaneous study within mixture studies (Maffini & Neltner, 2015), which at present are rare and sorely needed (Sarigiannis & Hansen, 2012). Third, there have been no systematic reviews of the developmental neuroimaging literature on metals, pesticides, flame retardants, phthalates, bisphenols, polychlorinated biphenyls, or solvents–all of which are systematically reviewed here. Given the rapidly growing body of research in this area, this review also acts as an update to the most recent systematic reviews

of imaging and air pollution (Balboni et al., 2022; de Prado Bert et al., 2018; Herting et al., 2019).

In sum, the present review has 4 goals: (1) describe the current state of the MRI literature on childhood toxicant exposure, (2) describe trends in findings within toxicant classes, (3) provide evidence regarding which toxicants have similar effects on the developing brain, and (4) provide productive avenues for future research.

2. Methods

This investigation followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). On August 3, 2022, an English-language search was conducted in PubMed and Scopus for the period spanning January 1, 2000 to August 3, 2022. Search terms were prepared by the lead author, reviewed by co-authors, and refined with the help of a Science Librarian at Duke University. Search terms can be found in the Supplement.

To ensure that all relevant studies were included in the present review, our formal search was complemented by examining the reference lists of existing narrative and systematic reviews on toxicant exposure and MRI-assessed brain function and structure in developing populations. We reviewed reference lists from peer-reviewed, published reviews available in English that appeared in our formal search or that were previously known to the authors.

Reference lists reviewed were: Balboni et al. (2022), Herting et al. (2019), and de Prado Bert et al. (2018)—systematic reviews of the imaging literature on air pollution; Rauh & Margolis (2016)—a narrative review tying lead and pesticide exposure to children's mental health and brain development; and Horton et al. (2014)–a narrative review of studies linking prenatal or childhood exposure to lead, pesticides, and tobacco smoke to brain structure and function. The present review expands on these works by being the first to systematically review the developmental neuroimaging literature on all toxicants under study except air pollution, by providing an update to the extant air pollution reviews' literature searches, and by integrating findings across the 9 toxicant classes included in the present review. The reference lists of some noteworthy reviews were not reviewed because they focused on associations between brain and exposure in non-human animals (Margolis et al., 2022), focused on non-environmental exposures (Dufford et al., 2021), focused on the aging brain (Power et al., 2016), or did not review imaging studies (Brockmeyer & D'Angiulli, 2016).

Inclusion criteria, established prior to conducting the literature search, were: (1) Study independent variable (exposure measure) must utilize direct or proxy assessments of exposure to suspected environmental or industrial neurotoxicants, including metals, solvents, flame retardants, polychlorinated biphenyls, bisphenols, organophosphate esters, phthalates, pesticides, parabens, per- and polyfluoroalkyl substances, and air pollutants (e.g., polycyclic aromatic hydrocarbons, particulate matter, nitrogen dioxide, ozone). Studies assessing primary or secondary exposure to medications and/or recreational drugs (e.g., tobacco smoking and second-hand smoke) were not considered, nor were studies of radiation exposure or light or noise pollution. (2) Study dependent variable (outcome measure) must

utilize MRI, including structural MRI (sMRI, e.g., T1 and T2 imaging), diffusion tensor imaging (DTI), magnetic resonance elastography (MRE), susceptibility weighted imaging (SWI), task functional MRI (fMRI), resting state fMRI (rs-fMRI), arterial spin labeling (ASL), and/or magnetic resonance spectroscopy (MRS). (3) Both exposure and outcome measures must be obtained prior to age 18. Studies with participants over age 18 were included only if the mean sample age at outcome assessment was below 18. Case studies, qualitative studies, animal studies, and studies not utilizing MRI were not considered.

A study protocol was developed and published on the Open Science Framework on May 15, 2021 (https://osf.io/qdwvp/). All studies were reviewed for inclusion criteria by at least two trained independent reviewers using the systematic review management tool Covidence (www.covidence.org). Study titles and abstracts were screened. Full text was read for studies that passed the screening stage.

After review, studies meeting inclusion criteria had the following data extracted by two independent reviewers: lead author, publication year, journal, study design, if part of a broader study (e.g., a cohort), toxicant class, toxicant measure, age at which toxicant measure was obtained, population studied, inclusion and exclusion criteria for MRI sample, number of MRI participants, age range, mean/median age, racial/ethnic composition, sex, MRI scanner type (e.g., 3T, 1.5T), MRI measure (e.g., sMRI, task fMRI, etc.), primary neuroimaging variables used in analyses, main effect of toxicant on the brain, and covariates used in analyses. Following data extraction, the lead author synthesized data by study characteristics and imaging findings. Meta-analysis was not used due to the small number of studies per toxicant and the heterogeneity of the MRI measures.

In addition to study data, study quality was assessed independently by two reviewers using the US National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). The Quality Assessment (QA) tool contained 14 items, such as “Was the participation rate of eligible persons at least 50%?” and “Was loss to follow-up after baseline 20% or less?” Questions were answered ‘yes’ (1), ‘no’ (0), or ‘NA’ by each independent reviewer. Studies earning scores of 10 or greater were deemed high quality, 6-9 deemed moderate quality, and 5 or fewer deemed low quality.

3. Results

Our search identified 1,158 studies, of which 107 were duplicates. 1,106 were excluded following title and abstract review, and 51 were advanced to full text review. During full text review, 5 further studies were excluded, resulting in a total N= 46 studies in this systematic review. Figure 1 presents a flow diagram of the search stages.

Figure 2 presents the number of studies published by year during the period under study (e.g., 2000 to 2022). Most studies on toxicant exposure and MRI measures of brain structure and function have been published in the last 5 years (i.e., since 2017; 30 studies, 65%).

Figure 3 presents the number of studies that investigated each class of toxicants. Air pollution received the greatest attention in the literature (19 studies; 41%), followed by

metals (12 studies; 26%), pesticides (4 studies; 9%), and multiple toxicants (4 studies; 9%). All other toxicant classes were investigated by 1 to 2 studies each.

Following NIH Quality Assessment Tool analysis, 10 (22%) studies were deemed high quality, 30 (65%) moderate quality, and 6 (13%) low quality. The primary reasons studies were rated as moderate or low quality included: recruiting convenience samples, failing to report effect sizes, retaining less than 80 percent of the sample at follow-up, and not making clear whether outcome assessors were blinded to exposure status. Quality assessment ratings by toxicant class are displayed in Figure 3.

3.1. Measures of toxicant exposure

Exposure measurement varied by toxicant class. Among the 19 studies on air pollution, air pollution was measured using land use regression or spatiotemporal modeling (N= 9; i.e., statistical extrapolation of air pollution exposure based on participants' home address and information about surrounding land use and pollution), high volume sampler (N= 4; i.e., a large, stationary monitoring device), combined use of backpack monitors and urine sampling (N= 1), combined use of backpack monitors and spatiotemporal modeling (N= 1), or comparison of children from a city with substantial air pollution (Mexico City) to those from a city with minimal air pollution (Polotitlan, Mexico) (N= 4).

Metals were measured via tap water samples from the child's home (N= 2), parent-report and tracking via hospital records (N= 1), lifetime residency in an area with versus without metal contamination (N= 1), deciduous teeth (N= 1), geocoded risk for exposure based on census tract (N= 2), and blood sampling (N= 4). Pesticides were measured via urine sampling (N= 2), cord blood at birth (N= 1), and life history calendars/parental status as a farmworker with pesticide exposure (N= 1). Flame retardants were measured via blood sampling (N= 2). Phthalates were measured via urine sampling (N= 2). All other toxicants (e.g., bisphenols, solvents, PCBs, and multi-toxicant exposure) employed the following measures: blood sampling (N= 1), cord blood at birth (N= 1), cord blood and umbilical tissue at birth (N= 1), urine sampling and blood sampling (N= 2), and urine sampling (N= 2).

3.2. Study location and samples

Figure 4 presents the geographic location of each study. All studies were conducted in high-income or middle-income countries. Most studies took place in Western Europe (19 studies, 41%) and the United States (16 studies, 35%). There were no published studies conducted in low-income countries or in South America, Africa, the Middle East, South Asia, or Oceania.

Many studies included in the present review used participants from the same samples. For example, 5 studies used the American Adolescent Brain Cognitive Development (ABCD) sample (Garavan et al., 2018), 6 studies used the Spanish Brain Development and Air Pollution Ultra Fine Particles in School Children sample (BREATHE) (Rivas et al., 2014), and 5 studies used the Dutch Generation R sample (Jaddoe et al., 2007). Only 9 studies (19.5%) used an independent sample not from a broader cohort. Figure 4 displays cohorts used in each of the 46 studies.

3.3. Age at exposure measurement and age at MRI

Figure 5a depicts the age group of children at the toxicant measure across studies. Age groups were based on Centers for Disease Control (CDC) guidelines (https://www.cdc.gov/ncbddd/childdevelopment/positiveparenting/index.html). It was most common for toxicant exposure to be measured prenatally, when mothers were pregnant with the child (N= 12). This was followed by at late middle childhood (N= 11; age 9-11), multiple time points (N= 9), lifetime residency in a polluted place (N= 5), at birth (N= 3), infancy (N= 2; age 1 and under), young adolescence (N= 2; age 12-14), preschool age (N= 1; age 3-5), and early middle childhood (N= 1; age 6-8). Figure 5b depicts children's age group at the MRI measure across studies. MRIs were conducted most often in late middle childhood (N= 20) and early middle childhood (N= 10).

3.4. Imaging findings

3.4.1. Air pollution—Air pollution describes the harmful gases and chemicals released into the air as a result of human activity (Mackenzie & Turrentine, 2016). Our search detected 19 studies on air pollution. Across these studies, the primary outcomes measured were differences in cortical white matter, cortical gray matter, subcortical gray matter, and brain function. More than one type of air pollution was measured in these studies, but for simplicity, these are referred to here only as air pollution. The type of air pollution measured as well as more study details can be found in Table 1. Air pollution studies reviewed had a wide range of sample sizes, ranging from fewer than 60 participants (N= 5) to more than 750 (N= 6).

White matter.: 14 air pollution studies examined associations with white matter (Table 1). 5 of these studies conducted whole brain analyses of white matter structure, and 2/5 found significant associations. Prenatal exposure predicted global reductions in white matter in early middle childhood, and age 5 exposure predicted reduced white matter in the prefrontal cortex (PFC) in the same period (Peterson et al., 2015). However, prenatal exposure predicted both smaller (inferior parietal lobes, cingulate) and larger (PFC, posterior inferior surface) volumes in a larger sub-sample of the same cohort when assessed in late middle childhood (Peterson et al., 2022). In contrast, first year of life exposure (Beckwith et al., 2020) and late middle childhood exposure (Pujol, Fenoll, et al., 2016; Pujol, Martínez-Vilavella, et al., 2016) were not associated with white matter volumes in young adolescence or late middle childhood, respectively.

5 studies assessed fractional anisotropy (FA)—a measure of white matter tract organization throughout the brain, and 3/5 found significant, but conflicting, results. In late middle childhood, greater cross-sectional exposure was associated with higher FA in and around the caudate nucleus (Pujol, Fenoll, et al., 2016), while across childhood and prenatal exposure was associated with lower FA in most white matter tracts in a different study (Lubczyńska et al., 2020). Also in late middle childhood, greater prenatal air pollution exposure was associated with higher FA in the basal ganglia and anterior cingulate (ACC) (Peterson et al., 2022). 2 studies found that cross-sectional exposure in late middle childhood was not associated with FA in any tract (Burnor et al., 2021; Pujol, Martínez-Vilavella, et al., 2016).

2 studies assessed mean diffusivity (MD)—a measure of the permeability of white matter tracts–and both found significant, but opposite, results. In a sub-sample (N= 7,602) of 9 to 10-year-olds from the American ABCD cohort, cross-sectional exposure was associated nonlinearly with reduced MD globally in the left hemisphere and in the left anterior thalamic radiations (ATR), left cingulum adjoining the hippocampus (CGH), left fornix (FX), left superior longitudinal fasciculus (SLF), right inferior longitudinal fasciculus (ILF), and bilateral uncinate fasciculus (UF), and was associated linearly with reduced MD globally in the right hemisphere and in the left inferior frontal occipital (IFO), left ILF, right CGH, and right FX (Burnor et al., 2021). In contrast, prenatal and average childhood exposure were associated with higher global MD in a sub-sample of 9 to 12-year-olds from the Dutch Generation R cohort (N= 2,954) (Lubczyńska et al., 2020).

2 studies used other measures of white matter microstructure, and both found significant results. Restricted isotropic intracellular diffusion (rNO)—a measure of diffusion within glia and cell bodies, restricted directional intracellular diffusion (rND)—a measure of diffusion within an axon, and hindered diffusion (hD)—a measure of extracellular diffusion were measured in Burnor et al. (2021). In this work in the ABCD cohort, cross-sectional exposure was associated with increased rNO in the bilateral UF, bilateral FX, left CGH, and left SLF, but it was not associated with rND or hD. Average diffusion coefficient (ADC)—a measure of the directionless rate of water at each brain voxel—was measured in Peterson et al. (2022), who found that greater prenatal exposure predicted differences in ADC across the cortex depending on the air pollutant.

The other white matter studies were ROI studies examining corpus callosum volume, white matter hyperintensities (e.g., lesions in the white matter), white matter volume of each lobe, and total cortical white matter volume. Of the studies of corpus callosum volume, 2/3 found significant associations. 2/2 found that prenatal air pollution exposure predicted smaller corpus callosum volume in late middle childhood (Lubczyńska et al., 2021; Mortamais et al., 2019), but, in Mortamais et al. (2019), the association did not survive correction for multiple comparisons. A third study comparing children from a polluted city (Mexico City) to those from an unpolluted city (Polotitlan, Mexico) did not find an association with corpus callosum volume (Calderón-Garcidueñas et al., 2012). The study on white matter hyperintensities and on white matter lobe volume also compared children from Mexico City and Polotitlan. Children from Mexico City had more white matter hyperintensities than children from Polotitlan (Calderón-Garcidueñas et al., 2008, 2011). Additionally, children from Polotitlan had greater white matter volume in bilateral temporal and right parietal lobes (Calderón-Garcidueñas et al., 2011) compared to children from Mexico City without white matter hyperintensities. However, Mexico City children with white matter hyperintensities had more white matter volume in the right parietal lobe than Mexico City children without hyperintensities.

Finally, all 4 studies assessing total cortical white matter volume (e.g., the summed volume of the white matter across the cortex) found null results. Cross-sectional (Cserbik et al., 2020), prenatal (Mortamais et al., 2019), and prenatal and across childhood (e.g., birth to MRI; Lubczyńska et al., 2021) exposures were not associated with total cortical white matter

volume in late middle childhood. Prenatal (Guxens et al., 2018) exposure was also not associated with total cortical white matter volume in early middle childhood.

Cortical gray matter.: 11 studies examined associations between air pollution exposure and cortical gray matter (Table 1). Whole brain analyses of cortical thickness, gray matter volume, and surface area were conducted. Total cortical gray matter volume of the entire cortex and of each lobe were studied as ROIs.

Mixed results were found for studies of air pollution and whole brain cortical thickness. 6/8 studies found significant results, but some studies found associations with both thicker and thinner cortex. Prenatal exposure was associated with thinner right frontal, right parietal, and left occipital lobes in early middle childhood (Guxens et al., 2018) and in late middle childhood (Lubczyńska et al., 2021), although both studies examined overlapping subsamples of the Dutch Generation R cohort at different time points. Mirroring these results, greater first year of life exposure was associated with thinner parietal and frontal cortices in American young adolescents (Beckwith et al., 2020). However, in contrast to these results, Peterson et al. (2022) found that prenatal exposure was associated with both thicker (lateral temporal, posterior inferior, and mesial) and thinner (dorsal parietal) cortices in late middle childhood. Further, in a smaller, younger sub-sample of the same cohort, Peterson et al. (2015) found no association between prenatal or age 5 exposure and cortical thickness in early middle childhood (Peterson et al., 2015).

Studies of late middle childhood exposure also produced mixed results. Exposure in this period was associated cross-sectionally with both thicker and thinner frontal, temporal, and cingulate regions (Cserbik et al., 2020), thinner supplementary motor cortex (Pujol, Fenoll, et al., 2016), and no change (Pujol, Martínez-Vilavella, et al., 2016). Average exposure from birth to late middle childhood was associated with thicker right post central gyrus and thinner left lingual gyrus (Lubczyńska et al., 2021). Finally, total cortical thickness was assessed by 2 studies (Cserbik et al., 2020; Lubczyńska et al., 2021). Neither found significant associations.

Studies of whole brain surface area were more consistent, with 2/2 finding significant associations. Late middle childhood exposure (Cserbik et al., 2020) was cross-sectionally associated with less surface area in frontal and occipital regions, while average exposure from birth to late middle childhood (Lubczyńska et al., 2021) was associated with less prefrontal surface area but greater surface area in several other brain regions. Prenatal exposure (Lubczyńska et al., 2021) was measured in one study of surface area, but the association with surface area was not reported. Total cortical surface area was only assessed by Cserbik et al., (2020) and was not associated with cross-sectional air pollution exposure in late middle childhood.

3 studies measured cortical gray matter volume via whole brain volumetric analysis, and 5 studied total cortical gray matter volume as an ROI. In the whole brain studies, first year of life exposure predicted reduced gray matter volume in the left parietal lobe in young adolescence (Beckwith et al., 2020), but late middle childhood exposure was not cross-sectionally associated with gray matter volume in any region (Pujol, Martínez-Vilavella,

et al., 2016). Total cortical gray matter volume was not associated with air pollution in any study (Calderón-Garcidueñas et al., 2011; Cserbik et al., 2020; Guxens et al., 2018; Lubczyńska et al., 2021; Mortamais et al., 2019).

Subcortical gray matter.: 10 of 19 studies on air pollution measured subcortical gray matter volume (Table 1). 3 studies employed whole brain volumetric analyses, and 2/3 found significant associations with subcortical structure. First year of life exposure predicted smaller bilateral cerebellum volume in young adolescence (Beckwith et al., 2020). Greater cross-sectional exposure predicted greater gray matter concentration in the caudate nucleus, a sub-region of the basal ganglia, in late middle childhood (Pujol, Fenoll, et al., 2016), but it was not associated with subcortical structure in a different study using the same sample (Pujol, Martínez-Vilavella, et al., 2016).

The remaining studies measured hippocampal, basal ganglia, and amygdala volume as ROIs. Studies of hippocampal and amygdala ROIs largely did not detect associations (Calderón-Garcidueñas et al., 2011, 2012; Cserbik et al., 2020; Guxens et al., 2018). In contrast, 6 of the ROI studies measured basal ganglia volume, and 3 found significant results. Reduced basal ganglia volume at late middle childhood was associated with cross-sectional exposure (Alemany et al., 2018; Cserbik et al., 2020; Mortamais et al., 2017). However, it was not associated with living in a polluted city (Calderón-Garcidueñas et al., 2011, 2012), or with prenatal and average air pollution exposure from birth to late middle childhood (Lubczyńska et al., 2021).

Brain function.: There were 6 studies on air pollution and brain function. (Table 1). 4 of these studies included MRS measures, and 3 found significant results. In American 6 to 14-year-olds, greater exposure to two air pollutants was associated with higher N-acetyl aspartate (NAA) and Choline (Cho) in the cingulate cortex (Peterson et al., 2015). Similarly, in an analysis of NAA, Cho, Cr (Creatinine), and myo-Inositol (mI) in the hippocampus, Mexican young adolescents with the e4 allele of the Apolipoprotein E gene and greater lifetime air pollution exposure had reduced NAA/Creatinine (NAA/Cr) ratio (Calderón-Garcidueñas et al., 2015). In contrast, in young American adolescents, greater past-year exposure to air pollution was associated with elevated mI in the ACC, but it was not associated with NAA, Cr, Cho, Glutamate (Glu), Glutamate and glutamine (GLX), or Glutathione (GSH) (Brunst et al., 2019). Finally, Pujol, Martinez-Vilavella et al. (2016) found no association between Cho/Cr ratio in the left frontal lobe and Spanish 8 to 12-year-olds' cross-sectional air pollution exposure.

Other brain function studies examined resting state functional connectivity, brain activation, and regional cerebral blood flow. All found significant results. 2 studies assessed cross-sectional exposures. In whole brain analyses of resting state fMRI and an fMRI task, greater cross-sectional exposure was associated with disrupted default mode network connectivity at rest, altered brain activation during a sensory stimulation task, and reduced resting state functional connectivity between the caudate and the frontal lobe in Spanish 8 to 12-year-olds (Pujol, Fenoll, et al., 2016; Pujol, Martínez-Vilavella, et al., 2016). 2 studies assessed prenatal and across childhood exposures. In Perez-Crespo et al. (2022), exposure from birth to age 3 was more likely to be associated with greater resting state functional connectivity

between several functional brain networks in Dutch Generation R participants than exposure at other time points. In Peterson et al. (2022), greater prenatal exposure was associated with lower regional cerebral blood flow in several cortical regions in American 6 to 14-year-olds.

3.4.2. Metals

Lead.: A heavy metal, widely known to be a developmental neurotoxicant, lead is often found in dust near roadways (Deocampo et al., 2012) and old homes (Wilson et al., 2022), in old paint and toys (Z. Shen et al., 2018), and in drinking water contaminated by lead pipes (Butler et al., 2016). Our search identified 6 developmental neuroimaging studies on lead. (Table 2).

Cortical gray matter structure was assessed in 3 lead studies (Kim et al., 2018; Marshall et al., 2020); 2/3 reported null findings. Kim et al. (2018) found null results when assessing the association between concurrent blood lead level and the cortical thickness of frontal lobe ROIs in 150 Korean children aged 6-17, while Marshall et al. (2020) found null results when assessing the cross-sectional association between risk of lead exposure and total cortical thickness, total cortical surface area, and total cortical volume (measured as ROIs) in roughly 9,000 American 9 to 10-year-olds from the ABCD cohort. However, also sampling from the ABCD cohort but with more participants (~10,000), Karcher et al. (2021) found that risk of lead exposure was associated with reduced total cortical thickness, total surface area, cortical gray matter volume, and intracranial volume.

Subcortical gray matter structure was assessed in 2 lead studies (Karcher et al., 2021; Marshall et al., 2021) both conducted in the ABCD cohort. 1/2 found significant results. Despite using the same sample, total subcortical gray matter volume was only associated with risk of lead exposure in Karcher et al. (2021). This is likely because Karcher et al. (2021) had the larger sub-sample from the cohort: N= 10,328 compared to N= 8,524 in Marshall et al. (2021). Additionally, Marshall et al. (2021) also measured the volume of the hippocampus, amygdala, ventricles, cerebellum, brain stem, and sub-regions of the basal ganglia. None of these were associated with risk of lead exposure.

Corpus callosum structure was assessed in 1 lead study (Marshall et al., 2021). In 10,328 9 to 10-year-olds from the ABCD cohort, greater risk of lead exposure was associated with smaller corpus callosum volume, except in the anterior sub-region.

Brain function was assessed in the other 2 lead studies, and both reported significant findings. Trope et al. (2001) reported that American children with elevated blood-lead levels (range: 23–65 μg/dL) had significantly lower NAA/Cr ratios in the left frontal lobe than children with never-elevated blood-lead levels. Similarly, Meng et al. (2005) reported that Chinese children with high concurrent blood-lead levels (mean: 37.7 μg/dL), compared to Chinese children with lower blood-lead levels (mean: 5.4 μg/dL), displayed reduced peak values of NAA, Cr, and Cho in the frontal lobes and hippocampus. Notably, these studies on brain function and lead had relatively small sample sizes: N= 21 (Trope et al., 2001) and N= 12 (Meng et al., 2005).

Manganese.: Manganese (Mn) exposure often occurs in mining or welding occupations (Flynn & Susi, 2009) or through contact with contaminated water (Eaton, 2021). Our search yielded 6 developmental neuroimaging studies on Mn exposure. Sample sizes were small, ranging from N= 12 (Iannilli et al., 2016) to N= 58 (Aschner et al., 2015). See Table 2.

Analyses of brain structure found that, in a sample of young adolescents, higher Mn exposure was associated with greater volume in the bilateral putamen, when cross-sectional ROI analyses of basal ganglia sub-regions were conducted (Lao et al., 2017).

Brain function in the context of Mn exposure was measured by 3 studies—all of which completed whole brain analyses, and all but 1 (Iannilli et al., 2016) analyzed resting state fMRI data. 3/4 studies found associations between metal exposure and basal ganglia function. Specifically, higher prenatal Mn exposure was associated with reduced resting state basal ganglia – PFC functional connectivity in 15 Mexican 6 and 7-year-olds (de Water et al., 2018; Pujol, Fenoll, et al., 2016). However, in another study of 14 Italian young adolescents, only postnatal Mn exposure—but not prenatal or childhood Mn exposure (as indexed by landmarks on deciduous teeth)—was associated with reduced connectivity between the basal ganglia and other brain regions (de Water, Papazaharias, et al., 2019). Finally, in the same sample of Italian adolescents as de Water, Papazaharias et al. (2019), whole brain analyses of task fMRI data revealed that higher lifetime Mn exposure was associated with reduced brain activation in olfactory and motor processing regions during an olfactory stimulation task (Iannilli et al., 2016).

Lastly, 2 of the Mn studies specifically examined T1 relaxation time, a measure of MRI signal intensity, in the basal ganglia, and both found significant associations with Mn exposure. Because Mn is paramagnetic, it appears as hyperintense on MRI images. This hyperintensity is associated with a shorter relaxation time, so a shorter relaxation time can indicate an accumulation of Mn in the brain in those at high exposure (Aschner et al., 2015). Correspondingly, in a study of newborn infants, infants with high recent Mn exposure had a shorter T1 relaxation time in the basal ganglia compared to infants at low Mn exposure (Aschner et al., 2015). In conflict with this result, however, a study of 9 to 15-year-old Canadians found the opposite: youth with higher concurrent Mn exposure had a longer T1 relaxation time in the basal ganglia (Dion et al., 2016).

3.4.3. Pesticides—

Pesticides are designed to control pests, weeds, and pathogens and prevent damage to crops and plants (Damalas & Eleftherohorinos, 2011). Our search yielded 4 MRI studies on pesticides. 2 studied brain structure, and 2 studied brain function. Sample size ranged from N= 40 (Rauh et al., 2012) to N= 518 (van den Dries et al., 2020). See Table 3.

In the structural studies, whole brain analyses of cortical thickness (Rauh et al., 2012; van den Dries et al., 2020), white matter (Rauh et al., 2012), and surface area (van den Dries et al., 2020) were conducted, as well as analyses of FA, MD, and volume of cortical and subcortical ROIs. Primary findings were associations with white matter. In (van den Dries et al., 2020), the authors found that prenatal exposure to organophosphate pesticides (OP)—a type of pesticide that disrupts the acetylcholine esterase enzyme—was associated

with reduced FA and higher MD—globally and in several white matter tracts in late middle childhood. In Rauh et al. (2012), greater prenatal exposure was associated with greater white matter volume throughout the cortex in early middle childhood. In contrast, no associations with whole brain cortical thickness, surface area, or any ROI was found in van den Dries et al. (2020), while thinner dorsal parietal and frontal cortex was associated with prenatal OP exposure in Rauh et al. (2012).

In the brain function studies, 1 study examined associations between prenatal OP pesticide exposure and whole brain activation during a motor inhibition task in 10 to 12-year-olds (Binter et al., 2020), while the other study assessed differences in resting state network organization between 8 and 9-year-old children of farmworkers and non-farmworkers (Bahrami et al., 2022). The task fMRI study found that prenatal OP exposure correlated with reduced PFC activation during the motor inhibition task in late middle childhood, while the resting state study found that farmworker children had altered default mode network (DMN) organization. Specifically, within the DMN, farmworker children had more connections between regions with higher clustering coefficients—a measure of connection strength—and fewer connections between regions with higher global efficiency—a metric that detects how quickly neural signals are sent between distant regions of the brain.

3.4.4. Flame retardants—Flame retardants are commonly added to furniture, clothing, electronics, infant products, and building materials to slow the rate at which these materials burn (Fromme et al., 2016). Our search yielded 2 developmental MRI studies on brain function and flame retardants (de Water, Curtin, et al., 2019; Margolis et al., 2020), and both found statistically significant associations with prenatal flame retardant exposure. (See Table 4). There are many types of flame retardants, but only the flame retardant class polybrominated diphenyl ethers (PBDE) has been studied in the context of the developing brain. Both studies measured brain function via neural global efficiency. In de Water, Curtin, et al. (2019), functional connectivity was examined via whole brain analyses, while in (Margolis et al., 2020) analyses were conducted for the reading network—a collection of frontal, tempo-parietal, and occipito-temporal regions in the left hemisphere that support reading (Margolis et al., 2020). Both studies were also conducted in the same cohort of 34 children from New York City (Horton et al., 2013). These studies reported that, in 5-year-old children, prenatal exposure to PBDEs was associated with (1) decreased global efficiency of the reading network, and (2) decreased global efficiency throughout the brain in regions associated with visual, auditory, and sensorimotor processing, but increased global efficiency in regions associated with learning and visual attention (de Water, Curtin, et al., 2019). In de Water, Curtin, et al. (2019), local efficiency, a measure of network segregation, was also measured, but no association with prenatal PBDE exposure was detected.

3.4.5. Plastics: phthalates and bisphenols—Phthalates are a form of plasticizer used in building materials, personal care products, food packaging, and medical tubing (Schettler, 2006). Bisphenols are plasticizers used to produce polycarbonates—hard, clear plastics—or epoxy resins, which can be found in baby bottles, food containers, and some dental products (Geens et al., 2012). Our search yielded 2 studies on phthalate exposure (England-Mason et al., 2020; Park et al., 2015) and 1 on bisphenol exposure (Grohs et

al., 2019). 2 of the studies (England-Mason et al., 2020; Grohs et al., 2019) examined white matter, measuring FA and MD of major white matter tracts in preschoolers, while 1 study (Park et al., 2015) measured whole brain cortical thickness in early middle childhood. Sample sizes ranged from N= 76 to N= 115. See Tables 5 and 6.

The 2 studies that focused on white matter measures both found that greater prenatal exposure to phthalates and bisphenols were associated with reduced FA and greater MD of white matter tracts at preschool age (England-Mason et al., 2020; Grohs et al., 2019), although the association in 1 study did not survive correction for multiple comparisons (Grohs et al., 2019). The third study (Park et al., 2015) focused on concurrent exposure to phthalates and whole brain cortical thickness in early middle childhood, finding an association between higher exposure and reduced cortical thickness in the temporal lobe.

3.4.6. Polychlorinated biphenyls—Polychlorinated biphenyls (PCBs) are legacy industrial contaminants that were once used as coolant fluids in electrical transformers or as sealants in caulks and paints; although no longer used in the U.S., they persist in the environment because of their long biological half-life (Carpenter, 2006). Our search yielded only 1 study on PCBs (Stewart et al., 2003), which assessed whether high versus low prenatal exposure to PCBs was related to the size of sub-regions of the corpus callosum in early middle childhood (N= 60 children; see Table 7). No significant associations were reported.

3.4.7. Solvents—Our search yielded 1 study (Table 8) on solvent exposure and brain function (Binter et al., 2019). The authors studied glycol ethers—a type of organic solvent used in paint, varnish, ink, cosmetics, and agriculture. Exposure was assessed prenatally, and whole brain activation patterns during a motor inhibition task were assessed in 71 French 10 to 12-year-olds. When inhibiting responses (whether correctly or not), higher exposure correlated with greater activation in the right precuneus and left cuneus; when successfully inhibiting responses, greater exposure was associated with reduced activation in left temporal and medial prefrontal regions and increased activation in right inferior frontal regions.

3.4.8. Exposure to more than one toxicant class (multi-toxicant exposure)—Our search yielded 4 studies that measured more than one toxicant class (Table 9) (C.-Y. Shen et al., 2021; Sussman et al., 2022; Weng et al., 2020; White et al., 2011). Weng et al. (2020) conducted whole brain resting state fMRI analyses in a sample of 59 adolescents about whom they also had information about their prenatal exposure to phthalates, cadmium, arsenic, per- and polyfluoroalkyl substances (PFAS), and methylmercury. Associations were found between prenatal exposures to methylmercury and PFAS and altered functional connections between the basal ganglia and other brain regions. For PFAS, these associations held even when controlling for exposure to heavy metals and phthalates. In a sub-sample of 49 adolescents from the same cohort, C.-Y. Shen et al. (2021) assessed associations between prenatal exposure to the same toxicants and white matter micro-structure and gray and white matter volume. Exposures were generally negatively associated with brain volumes, general fractional anisotropy and normalized quantitative anisotropy (measures of white matter fiber

tract organization), but positively associated with the isotropic value of the orientation distribution function (a measure of disorganized diffusion).

In White et al. (2011), associations between whole brain activation and prenatal exposure to PCBs and methylmercury in 6 Faroese 15-year-old boys were assessed. Combined exposure to both, compared to low exposure to both, was associated with greater bilateral activation —compared to expected unilateral activation—during a photo stimulation task and a finger tapping task. In Sussman et al. (2022), prenatal exposure to PCBs and PBDEs were assessed in 46 Canadian 9 to 11-year-olds. In an ROI analysis of right inferior frontal cortex (IFC), right anterior insula (AI), and bilateral supplementary motor area activation during an inhibitory control task, prenatal PCB exposure predicted decreased activation in the right IFC, while prenatal PBDE exposure predicted decreased activation in the right AI.

4. Discussion

In the present study, we reviewed all MRI studies published in the last 22 years (01/01/2000 – 08/03/2022) that examined the association between exposure to any known or suspected neurotoxicant and brain structure or function in youths under age 18 years.

One goal of the present review was to describe the current state of the literature. On this score, our review has produced several high-level findings. First, most studies on toxicant exposure and MRI-assessed measures of the developing brain have focused on a few toxicant classes—namely air pollutants and metals. Second, most studies were of moderate quality (65%), with few high quality (22%) and few low quality (13%) studies. Third, most studies were conducted in high-income, North American or Western European locations. Our search identified no studies from low-income countries, and no studies that took place in South America, Africa, the Middle East, South Asia, or Oceania. Fourth, this field is rapidly expanding: most articles (65%) reviewed here have been published since 2017. Fifth, it was most common for reviewed studies to measure toxicant exposure prenatally or at birth (32.6%) and to conduct imaging in late middle childhood (43.5%). Finally, few studies (19.5%) used a truly independent sample. Most research was conducted using participants from a few overlapping cohorts.

In addition to assessing the current state of the literature, the second goal of the present review was to describe trends in findings within toxicant classes. These are discussed in sections 4.1 - 4.7.

4.1. Air pollution

Across the air pollution literature, two trends emerged. First, regardless of age of exposure or age at MRI, summative measures of volume, thickness, and surface area did not seem to be associated with air pollution exposure. For example, 4 studies assessed associations between total cortical white matter volume (e.g., the summed volume of white matter across the cortex), and 0 detected associations between this variable and air pollution exposure regardless of timing of exposure (age 9-10, prenatal, average from birth to approx. age 10) or timing of MRI—although all MRIs were conducted in late middle or early childhood (Cserbik et al., 2020; Guxens et al., 2018; Lubczyńska et al., 2021; Mortamais et al., 2019).

Similarly, 5 studies assessed associations between total cortical gray matter volume (e.g., the summed volume of gray matter across the cortex), and 0 found associations between this variable and air pollution—despite measuring exposure at many different time points (at age 9-10, prenatally, as an average across childhood, across the first 2 years of life, as lifetime residency in a polluted area) and measuring cortical gray matter volume in late and early middle childhood (Calderón-Garcidueñas et al., 2011; Cserbik et al., 2020; Guxens et al., 2018; Lubczyńska et al., 2021; Mortamais et al., 2019). Finally, the evidence regarding mean total cortical thickness (e.g., mean thickness across the cortex) and total surface area (e.g., sum of surface areas of cortical brain regions) is weaker as both were only studied by the same 2 studies (Cserbik et al., 2020; Lubczyńska et al., 2021). However, both found null associations with air pollution. This does not mean, of course, that air pollution exposure is not associated with brain structure. Based on other findings from the present review, it likely means that different brain regions are impacted differently, creating a null additive result. Also, given that most studies had a large time lapse between assessing toxicant exposure and conducting brain imaging, it is possible that an effect exists, but measures of exposure and brain need to be closer together in time to detect it.

The second trend in the air pollution literature was that air pollution exposure was that cross-sectional exposure in late middle childhood was associated with reduced basal ganglia volume. 3 ROI studies examined associations between cross-sectional exposure to air pollution and basal ganglia volume in late middle childhood, and all 3 found the same result—smaller volumes in basal ganglia sub-regions (Alemany et al., 2018; Cserbik et al., 2020; Mortamais et al., 2017). In contrast, 3 other ROI studies of the basal ganglia and its sub-regions did not find significant results, but these studies examined exposure to air pollution in the prenatal period, as an average across all of childhood (e.g., from birth to late middle childhood), and by using lifetime residency as a proxy. Additionally, other subcortical ROIs (e.g., hippocampus, amygdala) were typically not associated with air pollution exposure. Only 1/5 studies found significant associations between air pollution exposure and other subcortical ROIs (Lubczyńska et al., 2021). One possible explanation for this pattern of results is that the basal ganglia may be more vulnerable to air pollution exposure than other regions of the subcortex. Parkinson’s disease—which is associated with the systematic degradation of the basal ganglia—has been associated with greater air pollution exposure in case-control studies (Fleury et al., 2021; Ritz et al., 2016). Moreover, the fact that the associations were observed for exposure occurring around age 10-11 could be due to the fact that this is a period of extremely rapid brain development coinciding with puberty (Blakemore et al., 2010), and the basal ganglia continue to develop into adolescence (Wierenga et al., 2014). However, these were ROI studies; whole brain studies are needed to empirically test the effects of exposure between brain regions.

4.2. Metals

The major trend evident in the extant metal literature was an association between exposure to Mn and disrupted basal ganglia structure and function. This association was present regardless of age of exposure or age at imaging and was present in 5/6 studies. It should be noted, however, that 3/6 studies on Mn studied the basal ganglia as an ROI, meaning that brain regions other than the basal ganglia might have been associated with Mn exposure

in these studies but were not identified. One explanation for this association could be that Mn deposits preferentially in the basal ganglia. Support for this hypothesis comes from the alterations in signal intensity associated with Mn exposure observed in the present review. Because Mn is paramagnetic, it shows up as hyperintense on MRI images of the brain, an indication of its neuro-accumulation (Aschner et al., 2015). Possibly, accumulation of Mn in the brain changes signal intensity, alters structure, and disrupts function.

4.3. Pesticides

For pesticides, emerging trends were challenging to identify because there were only 4 studies: 2 on brain structure and 2 on brain function. Within the brain function studies completely different metrics (whole brain activation in response to a task, organization of the default mode network) were employed, making results difficult to compare. On the other hand, within the 2 brain structure studies, both found associations between greater prenatal OP exposure and alterations in white matter in early (Rauh et al., 2012) and late middle childhood (van den Dries et al., 2020). However, even here these studies employed different white matter measures, with one assessing whole brain white matter via surface morphology, and the other assessing primarily MD and FA. If indeed white matter is more vulnerable to pesticide exposure, these changes may be explained by neuroinflammation. Rodent studies demonstrate that OP exposure increases inflammatory cytokines (Henderson et al., 2002) and activates microglia (dos Santos et al., 2016), which could trigger oxidative damage—to which white matter is vulnerable.

4.4. Flame retardants

In the flame retardant literature, the emerging trend was that greater prenatal exposure to PBDE flame retardants was associated with alterations in neural global efficiency—a measure of how quickly neural signals are transmitted between distant regions of the brain (de Water, Curtin, et al., 2019; Margolis et al., 2020). Although there were only 2 flame retardant studies yielded by the search, evidence for the specificity of this trend comes from the fact that 1 study (de Water, Curtin, et al., 2019) also measured local efficiency but did not find a significant association. Because neural global efficiency is supported by white matter integrity (McDonough & Siegel, 2018), these results may implicate the developing white matter. PBDEs' neurotoxicity may result from disrupted thyroid hormone function, damage from oxidative stress, or interference with calcium signaling and neurotransmission (Costa et al., 2014)—all of which could potentially damage white matter, and thus, alter global efficiency.

4.5. Plastics: bisphenols and phthalates

The literature on bisphenols and phthalates produced 2 primary findings: (1) greater prenatal exposure was associated with greater permeability (MD) and reduced organization (FA) of white matter tracts, and (2) greater childhood exposure was associated with differences in temporal lobe structure. Disruptions in thyroid hormone could explain these findings. Both phthalates and bisphenols have been observed to affect thyroid hormone (Ghisari & Bonefeld-Jorgensen, 2009; Moriyama et al., 2002). A well-recognized target of the thyroid hormone is the oligodendrocyte, the glial cell that makes and maintains the myelin sheath of the white matter (Anderson, 2001) and is particularly active during fetal and neonatal life

(Schug et al., 2015). This means that phthalate or bisphenol exposure could alter thyroid hormones, disrupting oligodendrocytes, and, in turn, early white matter development. However, both bisphenols and phthalates have also been observed to increase oxidative stress (Quagliariello et al., 2019; Waits et al., 2020). This process might better explain the decrease in cortical thickness of the temporal lobe found in Park et al. (2015), as decreases in cortical thickness have been previously attributed to neuronal death (Spear, 2013).

4.6. Polychlorinated biphenyls and solvents

For solvents and polychlorinated biphenyls, our search produced few trends. Only 2 studies, 1 on each toxicant, were yielded by the search: Binter et al. (2019) and Stewart et al. (2003). Binter et al. (2019) reported that prenatal glycol ether exposure correlated with altered activation throughout the brain during a motor inhibition task at school age. Mechanistically, one possibility is that glycol ethers may have a similar effect on the brain to another well-known solvent—ethyl alcohol—which alters brain development through acute toxicity and by increasing oxidative stress (Ehrhart et al., 2019). Indeed, Binter et al.'s (2019) findings mirror results reported in children with prenatal alcohol exposure (Ware et al., 2015). In contrast, regarding polychlorinated biphenyls (PCB), Stewart et al. (2003) reported no association between prenatal PCB exposure and splenium or genu size in school age children. PCB has been theorized to disrupt brain development by producing thyroid hormone dysfunction (Ghassabian & Trasande, 2018), but no alterations consistent with thyroid hormone dysfunction were observed.

4.7. Exposure to more than one toxicant class

Our search yielded 4 studies that measured more than one toxicant class: C.-Y. Shen et al. (2021) and Weng et al. (2020), both of whom measured prenatal lead, phthalates, PFAS, methylmercury, cadmium, and arsenic, Sussman et al. (2022) measured prenatal PCB and PBDE, and White et al. (2011) measured prenatal PCB and methylmercury. Possibly due to the different MRI measures assessed (e.g., 2 task fMRI studies employing different tasks, 1 resting state fMRI study, 1 DTI study), there were no clear trends evident in the results of these studies. Despite the different toxicants and neural outcomes studied, both PCB and PFAS are highly biologically persistent, and both are thought to impact brain development by disrupting thyroid function (Ghassabian & Trasande, 2018)—similar to flame retardants, phthalates, and bisphenols.

4.8. Evidence for similar effects of different toxicants

The third goal of the present review was to provide evidence regarding which toxicants have similar effects on the developing brain. This evidence could be used to inform which different toxicant classes might be good candidates for study together in cumulative effect or mixture studies, which are currently rare. Because youth are regularly exposed to more than one toxicant at once (Gaylord et al., 2020), understanding how exposures interact in their effects is critical (Sexton & Hattis, 2007). In the present review, toxicants with overlapping effects largely fell into two categories – those impacting the basal ganglia and those impacting white matter. First, manganese and air pollution were both associated with effects on the basal ganglia. In the case of manganese, these effects were associated with both brain structure and function, regardless of age at toxicant exposure (prenatal, infancy,

late middle childhood, adolescence all assessed) or age at MRI (infancy, early middle childhood, adolescence all assessed). In the case of air pollution, basal ganglia effects were mostly confined to effects on structure in late middle childhood. These associations may suggest a benefit of studying combined manganese and air pollution exposure in late middle childhood and measuring basal ganglia volume. Whole brain studies would be particularly beneficial, as these would help demonstrate if the associations hold when multiple brain regions are assessed. Two other groups of toxicants that might be good candidates for study together in cumulative effects studies are pesticides and flame retardants, as both displayed preliminary evidence of acting on white matter structure in the present review. Nevertheless, because few studies assessed the same toxicant and MRI measures at the same ages, comparisons of neurobiological effects across toxicants should be viewed with caution and will require future research to definitively address them.

4.9. On sensitive periods and exposures

Brain development occurs at a particularly rapid pace prenatally, in early childhood, and in adolescence (Johnson, 2001; Spear, 2008), and the brain may be more vulnerable to experience during these periods (Dunn et al., 2018; Gee, 2016). However, whether the brain is more vulnerable to toxicant exposure during periods of rapid maturation remains unknown. To determine this empirically would not only require multiple studies to measure exposures and brain outcomes at multiple time points, but also would require these studies to use the same brain outcome measure. Of 46 reviewed studies, 9 measured exposures at multiple time points, and only 1 measured the brain at multiple time points. Moreover, there was great heterogeneity among brain measures employed. For example, among studies measuring exposure prenatally (N= 12), the maximum number of studies that employed the same brain outcome measure at the same time point (e.g., fMRI task of inhibitory control in late middle childhood) was 3—and only 2 of these studies used the same task. Moreover, none of these studies measured the same toxicant exposure. Future longitudinal studies that begin in the prenatal period and measure both exposure and outcome across multiple time points are now needed to determine if neural sensitivity to toxicants differs based on developmental timing of exposure. Another possibility is that exposure may be harmful at certain critical windows of exposure that are unrelated to sensitive periods of brain development. Again, longitudinal studies with multiple measures of exposure and brain would help clarify.

4.10. Limitations

This review has limitations. First, we could not conduct a meta-analysis given the heterogeneity of study conditions (age groups, exposure measures, outcomes) and the small number of studies for some classes of toxicants. Second, we only reviewed English-language publications. Our search may not have detected studies that took place in countries where English is not the primary language for scientific writing and research.

In addition to these methodological limitations, the existing literature is also limited, and these limitations—in turn—constrain the reliability and generalizability of the conclusions of this review. Small sample sizes (e.g., $N \leq 60$), use of indirect exposure measures, and measurement of toxicants with short half-lives were all common in the studies included

in the present review. Small sample sizes reduce study power and precision of effect size estimates (Dick et al., 2021); use of indirect exposure measures may misclassify exposure; and, because toxicants with short half-lives (e.g., pesticides, phthalates, bisphenols, solvents) are metabolized and cleared from the body rapidly (Casas et al., 2018), exposure values for these toxicants are more likely to change. Because these practices may cause unreliability in the original studies, they make the inferences of this review less reliable. In addition, the field has yet to conduct any studies in low-income countries or in South America, Africa, the Middle East, South Asia, or Oceania. Moreover, most studies included in the present review drew from overlapping samples of existing cohort studies. 19 studies reviewed here came from just 4 cohorts: the American ABCD cohort, the Dutch Generation R cohort, the Spanish BREATHE cohort, and the American Columbia Center for Children's Environmental Health (CCCEH) cohort. In fact, only 9 studies reviewed did not specify sampling from an existing cohort. Given that many findings reported come from a handful of well-studied individuals in Western Europe and North America, this raises questions about the generalizability of the present findings. Moreover, it is possible that some of the cohorts themselves may have problems with generalizability. For example, the Dutch Generation R cohort deliberately oversampled children for prenatal exposure to drugs, alcohol, and psychiatric medication and with behavior problems. Even the ABCD study, which is impressive for its attempts at national representativeness, acknowledges that rural American youth may be under-represented (Garavan et al., 2018). Finally, most studies (65%) in the present review were of moderate quality, which may further constrain reliability and generalizability of the review.

4.11. Future directions

The fourth and final goal of this review was to determine avenues for future research. First, more studies are needed on toxicant exposure and developing brain structure and function, regardless of toxicant class, age at exposure, or age at MRI. Even looking within air pollution—the most studied toxicant in this review—there were few studies that had comparable study designs. For example, among 5 studies on air pollution and FA, only 3 studies measured cross-sectional associations between air pollution exposure and FA in late middle childhood. Yet, even within these studies there were key differences: one study had a sample size nearly 7 times the other two; one study measured air pollution exposure via hybrid spatiotemporal modeling, while the other two assessed exposure via a high-volume sampler; not all 3 studies even measured the same air pollutant (see Table 1). More studies with comparable designs, employing the same or similar MRI and toxicant measures and measuring both at the same or similar ages, are needed regardless of toxicant class. Until more studies are conducted, the findings in this systematic review remain preliminary and subject to change as more evidence comes available.

Further, some studies have received more attention in the literature than others. Bisphenols, flame retardants, phthalates, organophosphate esters, and parabens are widely present in children's homes and bodies (Frederiksen et al., 2013; Hoffman et al., 2018; Stapleton et al., 2009), but these toxicants have, to date, been investigated by no studies or by 1 to 2 studies each. More studies specifically on these toxicants are needed to elucidate how these toxicants interact with human brain development. Studies with comparable study designs

(e.g., assessing toxicant and brain at similar ages via similar measures) would be most helpful.

Across all toxicant classes, larger sample sizes, personal exposure monitoring, more studies with specific and independent populations are also all needed. One promising and low-cost personal exposure measure is silicone wristbands, which non-invasively and reliably (K. A. Anderson et al., 2017; O'Connell et al., 2014) measure personal exposure to many toxicants, such as flame retardants, pesticides, and some air pollutants (Dixon et al., 2018; Donald et al., 2016; Hammel et al., 2016). While more research on all age groups is necessary, the fewest studies to date have taken place in infants and preschoolers—even though these are periods of rapid brain development—and suggests the need for more studies specifically in these age groups. Additionally, given that only 9 studies used samples not drawn from existing cohorts and that some existing cohort studies may have problems with representativeness, more studies of independently recruited and representative samples are needed for all toxicants reviewed.

Further, even though a majority (26/46) of the studies yielded by the search were longitudinal, only 1 longitudinal study reported developing brain results at more than one time point (Calderón-Garcidueñas et al., 2012). Critically, longitudinal studies must also recruit representative samples, maintain excellent participant retention (e.g., 80 percent or more) between study waves, and report effect sizes—as problems on these points were some of the main reasons why studies were rated moderate quality and not high quality. More studies conducting MRI at multiple time points are needed to demonstrate the persistence of identified associations. Moreover, many studies conducted ROI analyses only, which may limit our understanding of the associations of exposures across the whole brain. More studies of whole brain associations are needed. Further, only 6/46 studies assessed developing brain structure and function with more than one imaging modality. Future studies might consider using multi-modal imaging analysis to provide a more comprehensive understanding of MRI phenotypes.

Finally, additional research should investigate toxicants and brain development in youth from low-income, non-Western nations. Because these countries have unique exposure patterns and sociocultural and economic contexts (Young et al., 2021), the field cannot assume that the associations observed in the present review will generalize to these nations, nor that toxicants deemed safe in one context at one dosage will be safe in all contexts. Our findings also suggest the importance of characterizing how diverse exposures interact in their effects. Only 4 studies yielded by our search assessed more than one toxicant class. Moreover, despite measuring multiple toxicants in a study, only 1 of the multi-toxicant exposure studies controlled for exposure to the other measured toxicants in their analyses to demonstrate the unique effect of an individual toxicant, and only 1 toxicant study expressly examined the effects of combined exposure. Multiple exposures may interact additively or synergistically, as has been found in the study of toxicants and the aging brain (Cabezudo et al., 2020). Researchers should test this hypothesis by collecting brain data and exposure data on diverse toxicants. Mixture modeling could assess which combinations of toxicants are most harmful. Such information would, in turn, be critical for proper regulation of individual toxicants and toxicant mixtures.

5. Conclusion

In this systematic review, we followed PRISMA guidelines to review the last 22 years of MRI studies on toxicant exposure and the developing brain. Associations were reviewed for 9 different toxicant classes. This is the first paper to systematically review the developmental neuroimaging literature on metals, pesticides, flame retardants, phthalates, bisphenols, polychlorinated biphenyls, solvents, and multi-toxicant exposure, as well as the first to integrate this literature with the literature on air pollution. Results revealed that most studies: (1) investigated air pollutants or metals, (2) assessed exposures prenatally and the brain in late middle childhood, (3) took place in North America or Western Europe, (4) sampled predominantly from a few cohort studies, and (5) have been published since 2017.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We conducted a systematic review following PRISMA guidelines of MRI studies investigating associations of toxicant exposure with youth brain structure and function published in the last 22 years (01/01/2000 – 08/03/2022).
- 9 toxicant classes were reviewed: air pollution, metals, pesticides, flame retardants, phthalates, bisphenols, polychlorinated biphenyls, solvents, and multi-toxicant exposure.
- Most reviewed studies (67%) studied air pollution or metals, assessed exposures prenatally (26%), and conducted neuroimaging in late middle childhood (43%).
- Most reviewed studies also took place in Western Europe or North America (78%), drew samples from existing cohort studies (80%), and have been published since 2017 (65%).
- More research on all toxicant classes reviewed here is needed. Future studies should also include larger samples, employ personal exposure monitoring, study independent samples in diverse world regions, and assess toxicant mixtures.

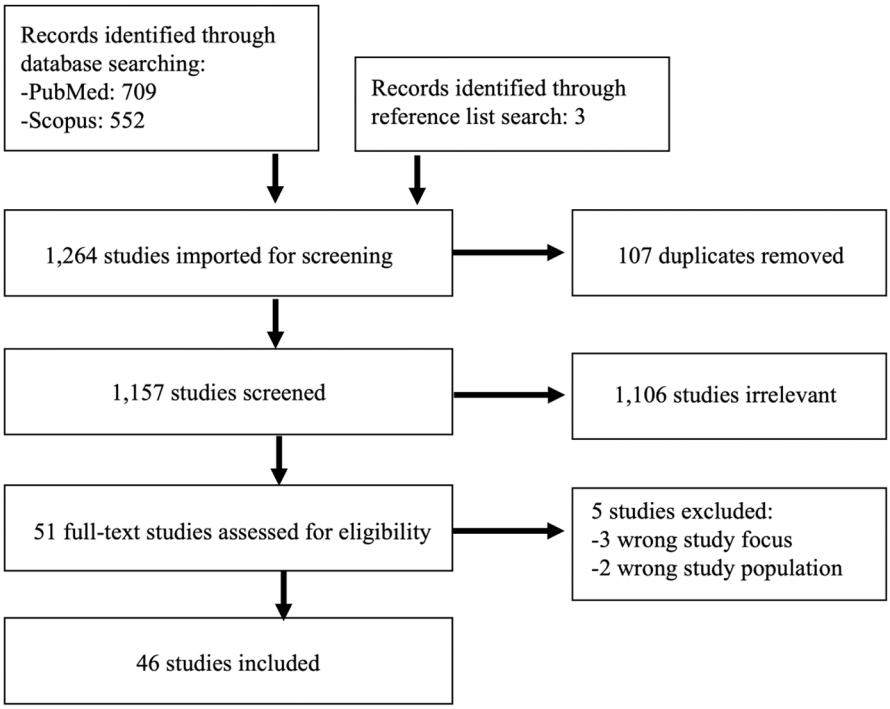

Figure 1.
PRISMA Flow Diagram.

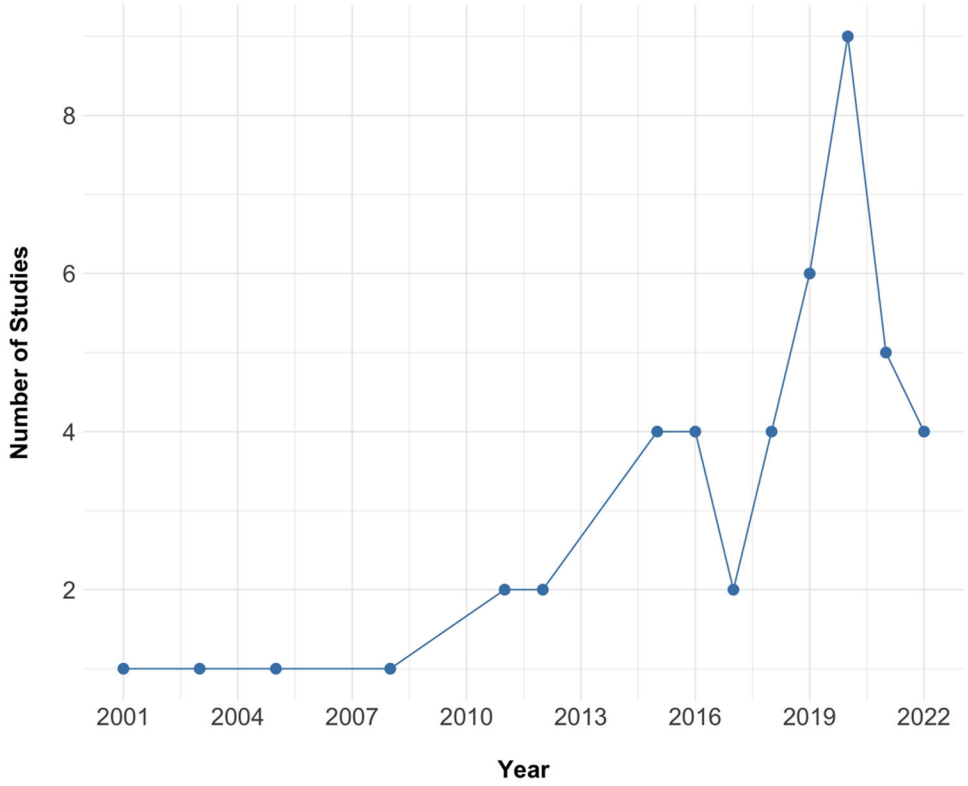

Figure 2.
Number of studies published on toxicant exposure and MRI-assessed measures of brain structure and function by year.

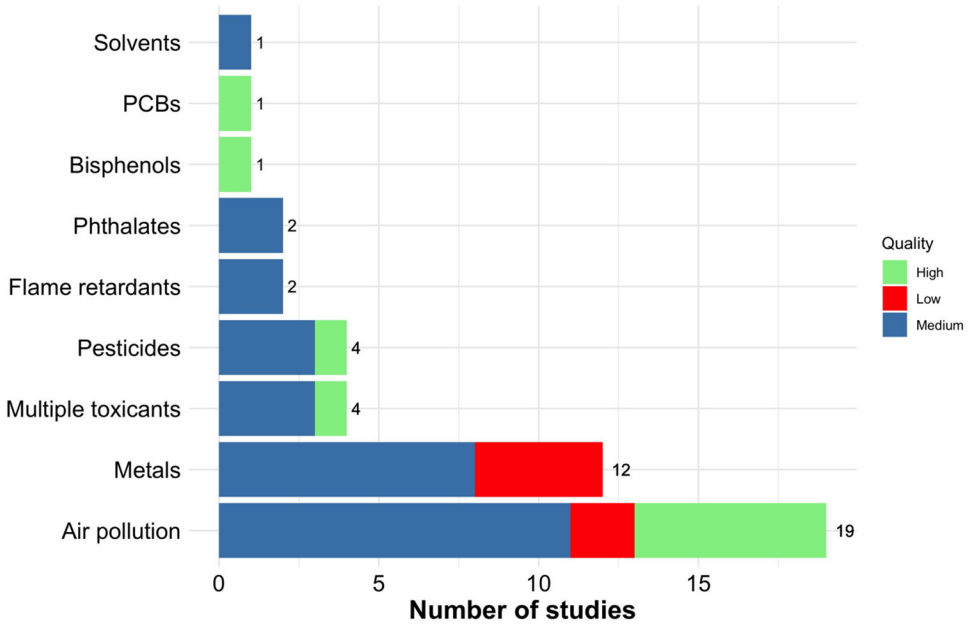

Figure 3.

Number of studies published on toxicant exposure and MRI-assessed brain development by toxicant class (01/01/2000 to 08/03/2022). Quality ratings are displayed on top of frequency counts. Numbers indicate the number of studies per toxicant class.

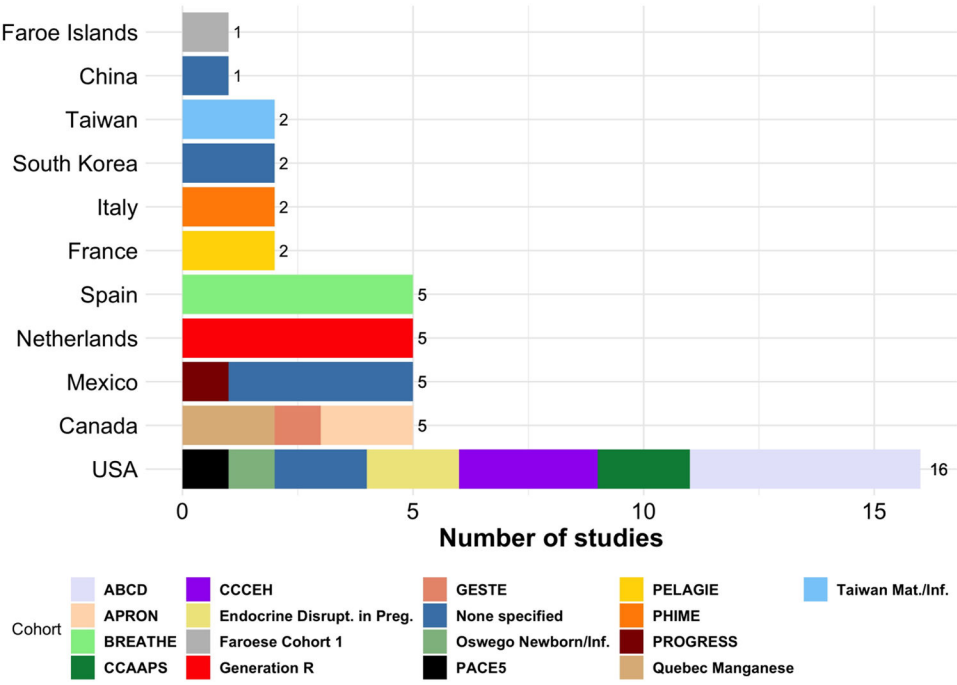

Figure 4.

Studies on toxicant exposure by study location (01/01/2000 to 08/03/2022). Numbers indicate studies per country. Legend displays which cohort samples were employed. Acronyms for cohorts can be found in the Supplement.

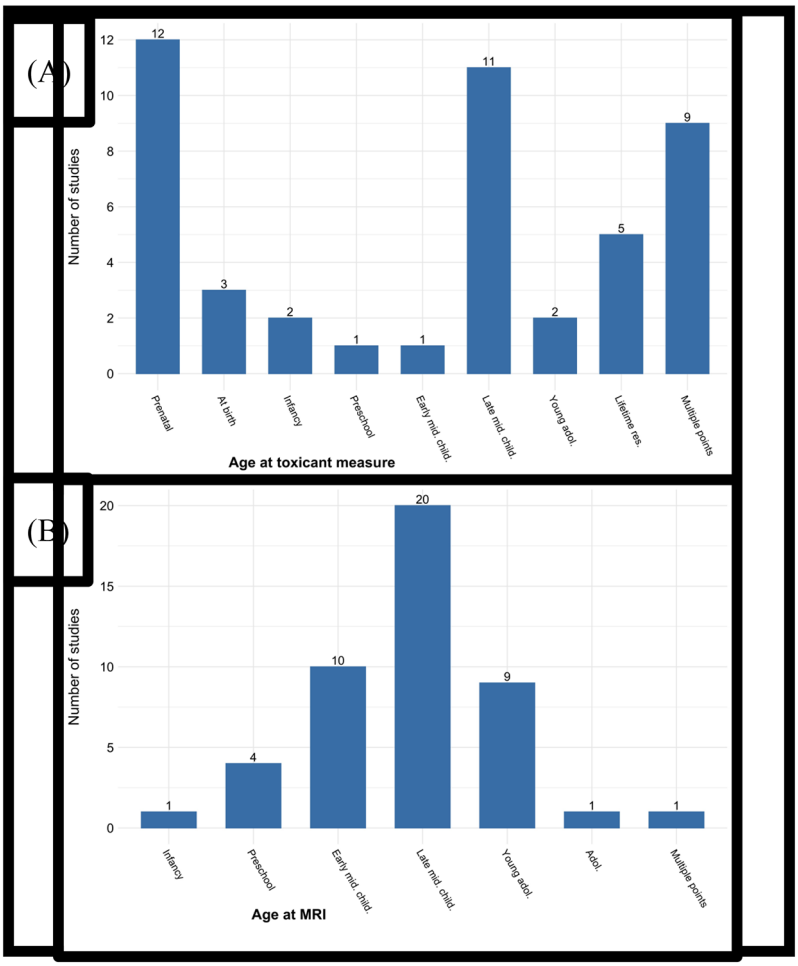

Figure 5.

Age at toxicant (A) and MRI (B) assessment. Lifetime res. refers to studies comparing children who lived in areas with different levels of pollution. Adol. = adolescence. Child. = childhood. Mid. = middle. Res. = residency. Age groups based on CDC guidelines.

Table 1.

Key findings and study characteristics of studies on air pollution exposure.

First author (study year)	Toxicant	N	Age at toxicant measure	Toxicant measure	Age at MRI	MRI measure	Exposure main effect
Alemany et al. (2018)	PAH, EC, and NO_2	163	7-11 years	High volume sampler	7-11 years	Basal ganglia vol. (caudate, putamen, globus pallidus)	Greater exposure to PAH and NO_2 associated with smaller caudate vol. only.
Beckwith et al. (2020)	ECAT	135	First year of life	Land use regression	11 – 14.71 years	Whole brain CT, Whole brain VBM	High ECAT group had reduced GMV in bilateral cerebellum and left parietal lobe, and thinner parietal and frontal cortex. No other associations.
Brunst et al. (2019)	ECAT	127	At birth, average from birth to MRI, average past year	Land use regression	At age 12 MRI visit	MRS voxel in bilateral ACC (metabolites : mI, NAA, Cr, Cho, Glu, GLX, GSH).	Elevated past year ECAT associated with elevated mI in bilateral ACC. No associations with other time periods or metabolites detected.
Burnor et al. (2021)	$PM_{2.5}$	7602	9-10 years	Hybrid spatiotempor al model	9-10 years	rND, hD, rNO, MD, FA of all white matter fibers in each hemisphere and of ATR, CGC, CGH, CC, CST, FX, UF, IFO, ILF, and SLF in each hemisphere.	Hemisphere-stratified models revealed positive associations between $PM_{2.5}$ and rNO in L hemisphere tracts (CGH, UF, FX, SLF) and R hemisphere tracts (UF, FX). Negative associations between $PM_{2.5}$ and MD globally, in L hemisphere tracts (ATR, CGH, FX, SLF, UF, IFO, ILF), and R hemisphere tracts (ILF, UF, CGH, FX). No associations with FA, rND, or hD.
Calderon-Garciduenas et al. (2008)	Air pollution (general)	36	N/A	Lifetime residency	*M*=10.71 years	WMH	7.6% of Polotitlan youth had WMH, vs. 56.5% from Mexico City.
Calderon-Garciduenas et al. (2011)	Air pollution (general)	30	N/A	Lifetime residency	*M*= 6.95 years	WMH, cortical GMV and cortical WMV of lobes, CSF, vol. of hippocampus, caudate, putamen, globus pallidus, amygdala	WMH^+ children (vs. WMH^-) had greater WMV in R parietal lobe. Polotitlan children had greater WMV in bilateral temporal and R parietal, lobes (compared to Mexico City youth). No associations with any other ROI.
Calderon-Garciduenas et al. (2012)	Air pollution (general)	30	N/A	Lifetime residency	*M*=7.13 years	WMH, combined GMV and WMV of lobes, vol. of frontal cingulate, parietal cingulate, cerebellum, CC, PFC, insula, hippocampus, caudate, putamen, globus pallidus, amygdala	Between baseline and follow-up, WMH^+ children had greater volumetric brain growth (GMV and WMV) in temporal, parietal, and frontal regions, compared to WMH-children. WMH^+ and Polotitlan children did not differ. No associations with other ROIs.
Calderon-Garciduenas et al. (2015)	Air pollution (general)	57	N/A	Lifetime residency	*M* = 12.45 years	MRS voxels in R and L hippocampus (metabolites : NAA, Cho, Cr, mI)	Children with APOE e4 genotype from Mexico City, compared to children from Polotitlan, had

First author (study year)	Toxicant	N	Age at toxicant measure	Toxicant measure	Age at MRI	MRI measure	Exposure main effect
							reduced NAA/Cr ratio in R hippocampus.
Cserbik et al. (2020)	$PM_{2.5}$	9697	9-10 years	Hybrid spatiotemporal model	9-10 years	31 SA regions, 27 CT regions, 8 subcortical vols, total SA, total CT, TBV, cortical GMV, subcortical GMV, cortical WMV, CSF, ICV, ventricle vols.	Greater $PM_{2.5}$ exposure associated with: (1) thinner L frontal, R temporal lobes; (2) thicker R frontal, L temporal lobes, (3) thicker and thinner bilateral cingulate, (4) reduced SA in R frontal pole, L cuneus, (5) greater SA in R lateral OFC, (6) greater R thalamus, R pallidum, L accumbens vol, (7) reduced L putamen, L pallidum vol. No other associations detected.
Guxens et al. (2018)	NO_2, particulate matter (coarse and fine particles), and absorbance of fine particles	783	Prenatal	Land use regression	6-10 years	Whole brain CT, TBV, cortical GMV, cortical WMV, subcortical GMV, vol. of caudate, putamen, pallidum, accumbens, hippocampu s, amygdala, thalamus, ventricles	Higher fine particle exposure associated with thinner R frontal, R parietal, and L occipital cortex. Higher coarse particle exposure associated with thinner R lateral OFC. Absorbance of fine particles associated with thinner L fusiform. No associations with any other measure.
Lubczynska et al. (2021)	NO_2, NO_x, PM_{10}, $PM_{2.5}$, PM_{coarse}, $PM_{2.5\ absorbance}$, PAH, BAP, OC, Cu, Fe, K, Si, Zn, OP, UFP	3133	Prenatal, average from birth to MRI	Land use regression	9-12 years	TBV, cortical GMV, subcortical GMV, cortical WMV, vol. of CC, cerebellum, thalamus, caudate, putamen, pallidum, hippocampus, amygdala, accumbens. Whole brain CT and SA.	Both thinner and thicker cortex associated with exposure, prenatally and across childhood, depending on region. Across childhood exposure associated with less PFC SA, but greater SA in other regions. No associations between pregnancy exposure and SA reported. Both pregnancy and across childhood exposure associated with smaller CC, smaller hippocampus , larger amygdala, larger cerebellum. No associations with other measures.
Lubczynska et al. (2020)	NO_2, NO_x, PM_{10}, $PM_{2.5}$, PM_{coarse}, $PM_{2.5\ absorbance}$, PAH, BAP, OC, Cu, Fe, K, Si, Zn, OP, UFP	2,954	Prenatal, average from birth to MRI	Land use regression	9-12 years	Global FA, global MD, follow-up analyses on individual white matter tracts	In single pollutant analyses, prenatal and average childhood exposure predicted lower FA and higher MD for many air pollutants assessed.
Mortamais et al. (2017)	Total sum of PAH levels, BAP	242	8-12 years	High volume sampler	8-12 years	Basal ganglia vol. (caudate, putamen, globus pallidus), brain parenchyma l fraction	Outdoor and indoor BAP predicted smaller caudate vol. Effect of total outdoor PAH on caudate vol. was similar but smaller than the effect of outdoor BAP. No other associations found.
Mortamais et al. (2019)	$PM_{2.5}$	186	Prenatal, average	Land use regression	8-11.7 years	Cortical GMV, cortical WMV, vol.	Greater 3rd trimester exposure linked to

First author (study year)	Toxicant	N	Age at toxicant measure	Toxicant measure	Age at MRI	MRI measure	Exposure main effect
			across first 2 years of life, time of MRI			of lateral ventricles and CC sub-regions	decreased vol. of anterior and body of CC. Associations did not survive correction for multiple comparisons. No associations with other ROIs or time periods.
Perez-Crespo et al. (2022)	NO_x, NO_2, $PM_{2.5}$, $PM_{2.5\ absorbance}$, PM_{10}	2197	Prenatal, 0-3, 3 – 6, 6 to time of MRI	Land use regression	9-12 years	Resting state functional connectivity of 6 brain networks	NO_2 from 0-3 and NO_x from 3-6 both associated with higher visual - task positive network connectivity. $PM_{2.5\ absorbance}$ from 0-3 associated with higher connectivity between visual and auditory, task positive, and task negative networks as well as between auditory and task positive and task negative networks, and between task positive and task negative networks. $PM_{2.5\ absorbance}$ from 0-3 also associated with greater connectivity within the visual, motor, task positive, and task negative networks. No other associations with other air pollutants or time periods.
Peterson et al. (2015)	PAH	40	Prenatal, at age 5	Personal backpack monitor for 48 hours; spot urine sample from child	7-9 years	Whole brain CT, surface morphology	Prenatal exposure to PAH correlated with reduced vol. in bilateral frontal, superior temporal, and parietal lobes and in L rostro-caudal extent of mesial surface —associations driven by changes in white matter. PAH at age 5 correlated with reduced WMV in bilateral dorsal PFC, especially SFG. No association with CT.
Peterson et al. (2022)	$PM_{2.5}$, PAH	332	Prenatal	Personal backpack monitor for 48 hours; spatiotempor al model	6-14 years	Whole brain CT, FA, ADC, MRS (metabolites: NAA, Cr, Cho, GLX), rCBF, surface morphology	PAH & $PM_{2.5}$ associated with (1) thicker lateral temporal, posterior inferior, and mesial wall cortices, (2) thinner dorsal parietal cortices, (3) smaller white matter vols in the inferior parietal lobes and cingulate gyrus, (4) larger white matter vols in dorsal convexity, SFG, and posterior inferior brain surface, (5) higher FA in basal ganglia and ACC, (6) lower rCBF in frontal gray matter, (7) higher NAA and Cho in cingulate. ADC alterations different for $PM_{2.5}$ vs. PAH.
Pujol, Fenoll et al. (2016)	Copper	263	8-12 years	High volume sampler	8-12 years	Whole brain CT,Whole brain VBM, FA, resting	Greater Cu associated with higher gray matter concentratio n in the

First author (study year)	Toxicant	N	Age at toxicant measure	Toxicant measure	Age at MRI	MRI measure	Exposure main effect
						state functional connectivity with seeds in PFC and caudate	caudate, greater FA in white matter in and around the caudate, diffusion changes in the caudate, reduced resting state functional connectivity between the caudate and frontal lobe operculum, and increased CT in L SMA.
Pujol, Martinez-Vilavella et al. 2016	Average of EC, NO_2	239	8-12 years	High volume sampler (EC), passive dosimeter (NO2)	8-12 years	Whole brain CT, Whole brain VBM, FA, brain activation during sensory task, resting state functional connectivity with seeds in medial frontal, dorsal frontal, PCC, and SMA, MRS voxel in L frontal lobe (metabolite:Cho/Cr ratio)	In the resting state analysis, higher exposure to air pollution was associated with weaker connectivity within DMN and stronger connectivity between the DMN and the lateral boundary of the DMN. In the task analysis, greater exposure to air pollution was associated with lower deactivations in the SMA and somatosensory cortex. No association with sMRI, FA, or MRS measures.

Note. See notes following Table 9 for table notes and a comprehensive list of abbreviations.

Table 2.

Key findings and study characteristics of studies on metal exposure.

First author (study year)	Toxicant	N	Age at toxicant measure	Toxicant measure	Age at MRI	MRI measure	Exposure main effect
Aschner et al. (2015)	Manganese	58	Newborn	Survey, medical and pharmacy records, blood sample	Newborn	T1R in globus pallidus, putamen	Greater parenteral nutrition and greater total Mn exposure associated with shorter T1R in globus pallidus and putamen. No association with whole blood Mn.
de Water et al. (2018)	Manganese	15	Prenatal	Blood sample	6.3 -7.6 years	Resting state functional connectivity with seeds in bilateral ACC, insula, MFG, superior parietal lobule, R and L globus pallidus	In children with higher prenatal Mn exposure, there was reduced R globus pallidus - dACC functional connectivity and a quadratic association between prenatal Mn and R globus pallidus-IFG connectivity. No other associations survived controlling for all covariates.
de Water, Papazahari as et al. (2019)	Manganese	14	Prenatal, early postnatal, and childhood	Deciduous teeth	12 – 18 years	Resting state functional connectivity with seeds in L and R putamen, L and R caudate, L and R pallidum, and bilateral MFG	Adolescents with higher early postnatal Mn exposure showed reduced functional connectivity between R putamen and L pre and post central gyri and increased bilateral MFG - L mPFC functional connectivity.
Dion et al. (2016)	Manganese	23	9- 15 years	Water sample from kitchen tap, questionnaire	9- 15 years	T1R in globus pallidus, standard PI, pericranial PI	High Mn group (vs. low Mn group) had lower signal intensity on the pericranial PI and longer T1R. No difference in standard PI.
Iannilli et al. (2016)	Manganese	14	N/A	Lifetime residency	14.65 years	Brain activation during olfactory stimulation task, olfactory bulb vol.	Whole brain task analysis: low Mn group had greater activation in secondary olfactory cortex, cerebellum, and SMA. ROI task analysis: low Mn group had greater activation in bilateral insula, R middle cingulate, and PCC. No association between Mn and olfactory bulb vol.
Karcher et al. (2021)	Lead	10,328	9-10 years	Geocoded lead risk	9-10 years	ICV, cortical GMV, subcortical GMV, total SA, total CT, hippocampa l vol	Lead risk associated with smaller ICV, subcortical GMV, cortical GMV, total SA, and total CT. Hippocampa l vol not associated with lead risk. Air pollution also assessed, but no analyses conducted with MRI measures.
Kim et al. (2018)	Lead	150	6 – 17 years	Blood sample	6 – 17 years	10-12 frontal lobe CT ROIs	No effect of lead on any ROI.
Lao et al. (2017)	Manganese	23	9-15 years	Water sample from kitchen tap	9-15 years	Basal ganglia vol. (caudate, putamen, globus pallidus) measured volumetrical ly and with mTBM	Using mTBM, high Mn group displayed larger L and bilateral putamen, but no difference when measured volumetrically.
Marshall et al. (2020)	Lead	9,712	9 – 10 years	Geocoded lead risk	9 – 10 years	Total CT, total SA,cortical vol.	No main effect of lead risk on any MRI measure.

First author (study year)	Toxicant	N	Age at toxicant measure	Toxicant measure	Age at MRI	MRI measure	Exposure main effect
Marshall et al. (2021)	Lead	8,524	9 – 10 years	Geocoded lead risk	9 – 10 years	Subcortical GMV, vol. of hippocampus, amygdala, cerebellum, brain stem, CC sub-regions, putamen, caudate, accumbens, pallidum, thalamus, ventricles	Lead risk associated with smaller CC in all sub-regions studied, except anterior CC. No other brain regions associated with lead risk.
Meng et al. (2005)	Lead	12	9 – 13 years	Blood sample	9 – 13 years	MRS voxel in L and R frontal lobe, L and R hippocampus (metabolites : NAA, Cr, Cho)	Peak of NAA, Cr, Cho lower in high lead group in all regions. For NAA, difference between high and low lead groups more pronounced in frontal lobe than hippocampus, and even more pronounced in R frontal lobe than L.
Trope et al. (2001)	Lead	21	Before age 5	Blood sample	8.75 years	MRS voxel in L prefrontal lobe (metabolites : NAA, Cr, Cho, ml).	The NAA/Cr ratio in the L prefrontal lobe was significantly lower in the high lead group.

Note. See notes following Table 9 for table notes and a comprehensive list of abbreviations.

Table 3.

Key findings and study characteristics of studies on pesticide exposure.

First author (study year)	Toxicant	N	Age at toxicant measure	Toxicant measure	Age at MRI	MRI measure	Exposure main effect
Rauh et al. (2012)	CPF	40	At birth	Cord blood	5.9 – 11.2 years	Whole brain CT, surface morphology	High CPF group showed enlarged bilateral temporal and parietal lobes and in R frontal and occipital lobes. Enlargement due to white matter. High CPF group had smaller dorsal and mesial SFG and thinner dorsal parietal and frontal cortices.
Binter et al. (2020)	OP metabolites	92	Prenatal	First morning void urine sample	10 – 12 years	Whole brain activation analysis of Go / No-go task	Higher metabolite levels associated with reduced PFC activation when successfully inhibiting.
van den Dries (2020)	OP metabolites (DM, DE)	474	Prenatal	3 spot urine samples	9 – 12 years	TBV, WMV, cortical GMV,subcortical GMV, vol. of CC, hippocampus, amygdala, caudate, thalamus, pallidum, putamen, accumbens. Whole brain CT and SA. FA and MD of tracts and globally.	No association with brain vol., CT, or SA. Higher metabolite levels associated with lower global FA and higher global MD. Higher DM associated with lower FA and higher MD in all tracts except L UF, forceps major, and R corticospinal tract. Higher DE associated with lower FA in L superior longitudinal fasciculus, corticospinal tract, and higher MD in L cingulate of cingulum, forceps minor, and L ILF.
Bahrami et al. (2022)	Pesticide (general)	78	Prenatal, 0-2 years, 3 – 8 years, 8-9 years	Life history calendar, parents work on farms or not	8-9 years	Resting state functional connectivity: clustering coefficient, connection strength, global efficiency within the DMN and globally.	No differences in clustering coefficient or connection strength across the entire brain, excluding the DMN, between farmworker vs. non-farmworker children. Within the DMN, farmworker children were more likely to have connections between regions with higher clustering coefficients and less likely to have connections between regions with higher global efficiency. These metrics were associated with higher childhood pesticide exposure in the same way.

Note. See notes following Table 9 for table notes and a comprehensive list of abbreviations.

Table 4.

Key findings and study characteristics of studies on flame retardant exposure.

First author (study year)	Toxicant	N	Age at toxicant measure	Toxicant measure	Age at MRI	MRI measure	Exposure main effect
De Water, Curtin et al. (2019)	PBDE	34	Prenatal	Blood sample	5 years	Whole brain GE, LE	Greater PBDE associated with increased GE in regions associated with learning and visual attention and reduced GE in regions associated with visual, auditory, and sensorimotor processing.
Margolis et al. (2020)	PBDE	33	Prenatal	Blood sample	5 years	GE of reading network	Greater PBDE associated with lower GE in the reading network. PBDE-47 and 153 contributed most to this association.

Note. See notes following Table 9 for table notes and a comprehensive list of abbreviations.

Table 5.

Key findings and study characteristics of studies on phthalate exposure.

First author (study year)	Toxicant	N	Age at toxicant measure	Toxicant measure	Age at MRI	MRI measure	Exposure main effect
England-Mason et al. (2020)	High and low molecular weight phthalates	76	Prenatal	Spot urine	3 – 5 years	FA and MD in major white matter tracts.	HMWP exposure was associated with greater MD of the R IFO, R pyramidal fibers, and bilateral UF. Higher LMWP exposure was associated with reduced FA of the L ILF.
Park et al. (2015)	Metabolites of DEHP and DBP	115	6 – 15 years	Spot urine	6 – 15 years	Whole brain CT	Negative correlation between metabolites of DEHP and CT in the right middle and superior temporal gyri.

Note. See notes following Table 9 for table notes and a comprehensive list of abbreviations.

Table 6.

Key findings and study characteristics of studies on bisphenol exposure.

First author (study year)	Toxicant	N	Age at toxicant measure	Toxicant measure	Age at MRI	MRI measure	Exposure main effect
Grohs et al. (2019)	Bisphenol A	98	Prenatal, age 3-4 years	Spot urine from mother and child	2 – 5 years	FA, MD of white matter tracts	Association between prenatal BPA and greater MD of splenium and R ILF, but this did not survive multiple comparisons. No association with age 3-4 BPA.

Note. See notes following Table 9 for a comprehensive list of abbreviations.

Table 7.

Key findings and study characteristics of studies of polychlorinated biphenyl (PCB) exposure.

First author (study year)	Toxicant	N	Age at toxicant measure	Toxicant measure	Age at MRI	MRI measure	Exposure main effect
Stewart et al. (2003)	PCB	60	At birth	Cord blood	~ 7.8 years	Size of genu, splenium	No association of PCB with splenium size. Association between genu and PCB not reported.

Note. See notes following Table S9 for table notes and a comprehensive list of abbreviations.

Table 8.

Key findings and study characteristics of studies on solvent exposure.

First author (study year)	Toxicant	N	Age at toxicant measure	Toxicant measure	Age at MRI	MRI measure	Exposure main effect
Binter et al. (2019)	Glycol ether metabolites:	71	Prenatal	First morning void urine	10-12 years	Whole brain activation analysis of go/no-go task	When inhibiting, moderate exposure was associated with greater activation in R precuneus, L cuneus, and R IFG. When successfully inhibiting, high exposure was associated with reduced activation in L temporal and medial frontal regions.

Note. See notes following Table 9 for table notes and a comprehensive list of abbreviations.

Table 9.

Key findings and study characteristics of studies on exposure to more than one toxicant class.

First author (study year)	Toxicant	N	Age at toxicant measure	Toxicant measure	Age at MRI	MRI measure	Exposure main effect
White et al. (2011)	PCB, MeHg	6	At birth	Umbilical cord tissue and cord blood	14 – 15 years	Activation analyses from photic stimulation task and finger tapping task	During the photic stimulation task, the high exposure group had greater activation in bilateral visual association areas and in R temporal and frontal lobes. During the finger tapping task, the high exposure group had greater activation in bilateral premotor and motor cortex, compared to the low exposure group whose activations were largely one-sided in motor regions.
Weng et al. (2020)	Phthalates , cadmium, arsenic, lead, MeHg, types of PFAS	59	Prenatally	Spot urine sample, blood sample	13 – 16 years	mFALFF, mReHo	Higher phthalate exposure was associated with reduced mFALFF in R SFG and MFG and increased mReHo in L medial and inferior temporal gyrus; higherPFOS was associated with reduced mFALFF in R putamen and insula; higher PFNA with reduced mReHo in bilateral putamen and L caudate; higher lead with greater mFALFF in bilateral cuneus; higher MeHg with greater mFALFF in L superior temporal gyrus and decreased mReHo in R putamen and caudate.
Shen et al. (2021)	Phthalates , cadmium, arsenic, lead, MeHg, types of PFAS	4 9	Prenatally	Spot urine, blood sample, cord blood at birth	13 – 16 years	Whole brain VBM, GFA, NQA ISO	Phthalates, perfluorochemicals , and heavy metals were negatively associated with cingulate, cerebellum, frontal, temporal, hippocampal, and calcarine gyrus vol, CC, corona radiata, SLF, external capsule vol. Perfluorochemicals and heavy metals were negatively associated with GFA and NQA in the CC and internal capsule. Heavy metals were positively associated with ISO in CC external capsule, SFO, and SLF.
Sussman et al. (2022)	PCB, PBDE	46	Prenatally	Blood sample	9-11 years	ROI analyses of R IFC, SMA, R AI from Simon spatial incompatibility fMRI task	On incongruent > congruent trials, higher exposure to 2 PCBs and their sum was associated with decreased activation in the right IFC, and higher exposure to PBDE was associated with decreased activity in the rAI. No other associations detected.

Note. Abbreviations are as follows. Abbreviations articulated earlier in the paper are not repeated. ADHD = attention deficit hyperactivity disorder. BAAN = benz[a]anthracene. BAP = benzo[a]pyrene. BEP – benzo[e]pyrene. BGP = benzo[g, h, ijperylene. CHRYS = chrysene. CPF = chlorpyrifos. CSF = cerebrospinal fluid volume. CST= corticospinal tract. CT = cortical thickness. DAP = dialkylphosphate. DBP = di-n-butyl phthalate. DE = diethylphosphate. DEHP = di(2-ethylhexyl) phthalate. DM = dimethylphosphate. EC = elemental carbon. ECAT = elemental carbon due to traffic. Fe = iron. GE = global efficiency. GFA = generalized fractional anisotropy. GMV = gray matter volume. ICV = intracranial volume. HMWP = High molecular weight phthalates. IFG = inferior frontal gyrus. ISO= isotropic value of the orientation distribution function. K = potassium. L = left. LE = local efficiency. LMWP = low molecular weight phthalates. MeHg = methylmercury. mFALFF = mean fractional amplitude of low frequency fluctuations. MFG = medial frontal gyrus. mPFC = medial prefrontal cortex. mReHo = mean regional homogeneity. mTBM = mean tensor-based morphometry. NICU = neonatal intensive care unit. $N0_2$ = nitrogen dioxide. Nox = nitrogen oxides. NQA = normalized quantitative anisotropy. OC = organic carbon. OFC = orbitofrontal cortex. OP = oxidative potential of PM2.5· PAH = polycyclic aromatic hydrocarbons. PCC= posterior cingulate cortex. PFOS = perfluorooctane sulfonate. PI = pallidal index. R = right. rCBF = regional cerebral blood flow. RN = reading network. SA = surface area. SFG = superior frontal gyrus. Si = silicon. SMA = supplementary motor area. TBV = total brain volume. T1R = T1 Relaxation time. UF = uncinate fasciculus. UFP = ultra-fine particles. VBM = voxel-based morphometry. Vol = volume. WMV = white matter volume. WMH = white matter hyperintensities. WMH^+ = positive for presence of white matter hyper-intensities. WHM^- = negative for presence of white matter hyperintensities. WMV = white matter volume. Zn = zinc.