Review

Biological Psychiatry: GOS

Neurotoxicants, the Developing Brain, and Mental Health

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ABSTRACT

While life in urban environments may confer a number of benefits, it may also result in a variety of exposures, with toxic consequences for neurodevelopment and neuropsychological health. Neurotoxicants are any of a large number of chemicals or substances that interfere with normal function and/or compromise adaptation in the central and/or peripheral nervous system. Evidence suggests that neurotoxicant effects have a greater effect when occurring in utero and during early childhood. Recent findings exploring neural-level mechanisms provide a crucial opportunity to explore the ways in which environmental conditions may get "under the skin" to impact a number of psychological behaviors and cognitive processes, ultimately allowing for greater synergy between macro- and microlevel efforts to improve mental health in the presence of neurotoxicant exposures. In this review, we provide an overview of 3 types of neurotoxicants related to the built environment and relevant to brain development during childhood and adolescence: lead exposure, outdoor particulate matter pollution, and endocrine-disrupting chemicals. We also discuss mechanisms through which these neurotoxicants affect central nervous system function, including recent evidence from neuroimaging literature. Furthermore, we discuss neurotoxicants and mental health during development in the context of social determinants and how differences in the spatial distribution of neurotoxicant exposures result in health disparities that disproportionately affect low-income and minority populations. Multifaceted approaches incorporating social systems and their effect on neurotoxicant exposures and downstream mental health will be key to reduce societal costs and improve quality of life for children, adolescents, and adults.

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Within the past century, and increasingly in recent decades, more of the population has shifted to living in more urban city settings, up from 40% of the United States population in 1900 to 83% in 2018 (1). While cities and large urban areas can confer a large number of benefits, such as more diverse social networks, well-developed infrastructure, and access to resources and opportunities for social support (2), they also may subject inhabitants to a large number of exposures that may have repercussions for their physical and mental health. In addition, owing to the complex and dynamic spatial properties of cities, urban development is widely heterogeneous, leading to spatial and socioeconomic inequity in how these exposures are distributed (3), therefore making the issue of negative urban exposures and health of interest to epidemiologists, sociologists, and biologists alike.

Although environmental exposures in cities have been documented to have a number of effects on physical health, research on their impacts on mental health has, until recent years, been fairly scarce (4). In particular, recent findings have highlighted the importance of childhood environmental exposures on neurodevelopment (5), providing an additional piece of the complex puzzle through which these exposures may affect mental health. Recent neuroimaging methods have offered an opportunity to interrogate the ways in which various environmental exposures can get "under the skin" to affect neural structure and function. Thus, the focus of this review is to present current evidence supporting toxic childhood environmental exposures that affect neural structure and function, referred to here as neurotoxicants, and their impact on mental health.

Neurotoxicants are any chemicals or substances that interfere with normal function and/or compromise adaptation in the central and/or peripheral nervous system, either during development or at maturity (6,7). This definition may apply to more than 200 chemicals reported as neurotoxicants in humans (8), ranging from metals and inorganic compounds to air pollution to organic solvents (see http://braindrain.dk/known-chemical-brain-drainers/ for a list of known neurotoxicants). An additional key point from this definition is that it highlights time of exposure during development as critical to the severity of neurotoxicant effects, with increased vulnerability occurring in utero and during early childhood (9). While several effects have been reported for neurotoxicant exposures in adulthood, low levels of exposure during key developmental periods may be enough to cause irreparable brain injury. To reduce societal costs and improve quality of life for affected individuals, research on modifiable risk factors holds the promise to open new avenues for early prevention and intervention.

In the following sections, this article highlights 3 neurotoxicant exposures related to the built environment: lead exposure, outdoor particulate matter (PM) pollution, and

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endocrine-disrupting chemicals (EDCs). We will also discuss candidate mechanisms identified in the literature on how these neurotoxicants affect central nervous system (CNS) function and relate to neuropsychological mental health disruptions, with a particular focus on noninvasive neuroimaging results. While this article is not a systematic review of the literature on neurotoxicants, our goal is to bring awareness to the various ways in which certain environmental exposures that are often found in urban settings can impact individual-level neuropsychological development and function, so as not only to inspire change at legislative levels but also to leverage efforts of individuals within their communities by providing knowledge that may aid in advocating for their wellbeing. Furthermore, we would like to acknowledge that most (if not all) negative neurotoxicant exposure associations with mental health are exacerbated in racial and ethnic minority and low-income children (5), and although the coverage of the structural and social determinants of mental health involved are outside the scope of this article, further research is needed to interrogate the particular upstream mechanisms (e.g., institutionalized discriminatory practices, environmental racism) that give rise to these unequal exposures and disparities (10).

LEAD EXPOSURE

Relevance to Public Health

Metals are one of the most widely studied, and concerning, set of neurotoxicants, with annual costs for lead poisoning and methylmercury toxicity estimated at $60 billion in 2008 (11). Lead-based poisoning is particularly alarming given that evidence has shown that any amount of detectable lead can be harmful to neuropsychological outcomes at all ages (12). In 2021, the Center for Disease Control and Prevention updated the blood lead reference value to 3.5 μg/dL to identify children at ages 1 to 5 years in the top 2.5 percentile of blood lead level (BLL) distribution (13). Over the past decades, environmental legislation in the United States has dramatically reduced the number of cases of lead poisoning in children ages 1 to 5, from 88% in 1976–1980 to 0.8% during 2007–2010, using a BLL cutoff of ≥10 μg/dL (13). Yet, as of 2017, about 500,000 U.S. children are currently affected by elevated BLLs using a more stringent cutoff of ≥5 μg/dL (14). As is the case with many environmental neurotoxicants, the highest burden of lead poisoning is experienced by minority populations, with Black children being twice as likely to have elevated BLLs than White or Latinx children (15), highlighting the undeniable effect of upstream structural and sociopolitical factors in the distribution of neurotoxicant exposures.

Sources of Exposure

Sources of lead-based poisoning include lead-based paint in older homes, contaminated drinking water pipes, and residual lead in soil deposited from airborne emissions, which can recontaminate areas (16) (Figure 1; Table S1).

Potential CNS Mechanisms

Lead does not seem to have any known physiological functions (17) but is able to cross the blood-brain barrier, thereby interfering with the functioning of many processes in the CNS (18). Based on limited studies in humans and many studies in rodents and nonhuman primate systems, lead seems to heavily affect dopaminergic neurotransmission. Primarily, studies in rats indicate that chronic exposure to lead may result in increased dopamine release in the nucleus accumbens while reducing synaptic clearance of dopamine (19,20). Studies on lead exposure have also indicated increased sensitivity in dopamine D_1/D_2 receptors, with possible additional disturbances in glutamate/dopamine interactions (21), although this

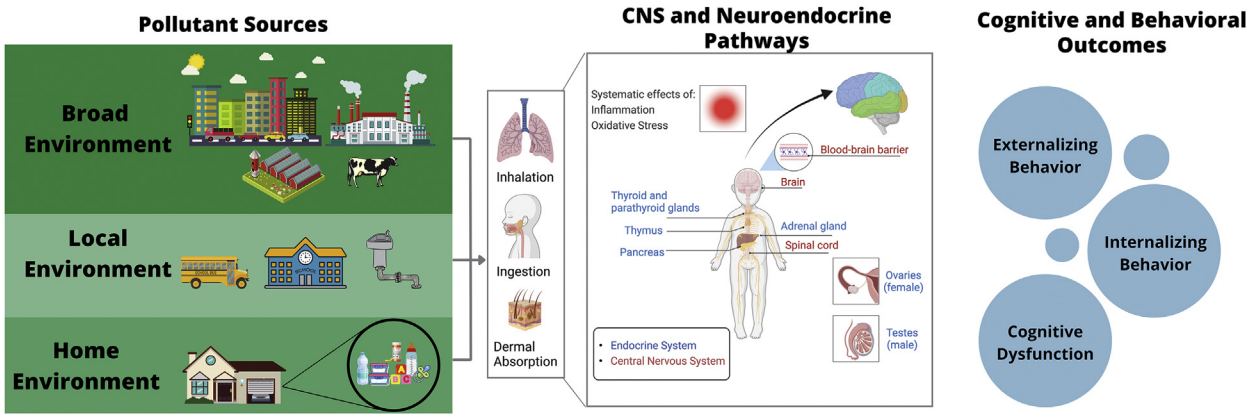

Figure 1. Sources of major neurotoxicants and proposed physiological targets. Exposure to the 3 classes of neurotoxicants discussed in this article (lead, outdoor particulate matter air pollution, and endocrine-disrupting chemicals) can occur through multiple avenues, because the sources for these toxicants include broad environmental pollution from traffic, agriculture, industrial activities, etc.; local pollution in areas, such as parks and schools, where children spend time; and home pollution, where children may be exposed to household items containing neurotoxic chemicals. These pollution sources, encountered in children's broad and local environments, may enter the body through inhalation, ingestion, and/or dermal absorption (see Table S1 for further details). Once in the bloodstream, these toxicants may cross the blood-brain barrier and directly act upon components of the central nervous system (CNS) or indirectly affect the brain by altering other systems, including air pollution–related increases in inflammation and oxidative stress or endocrine-disrupting chemicals acting to disrupt the endocrine system. A causal arrow is not drawn between the physiological diagram and the behavioral and cognitive outcomes, because no causal link has been confirmed. However, it is hypothesized that disruption of normal neurodevelopment and damage to neural and endocrine pathways may lead to changes in behavioral symptoms, cognitive development, and mental health in children.

may be dependent on the level of the dose, sex, and developmental stage of exposure, with earlier exposures resulting in stronger perturbations to dopaminergic systems (17,20,21). Furthermore, murine models of lead exposure and dopaminergic system perturbations have also indicated an enhanced sensitivity to rewarding stimuli and drugs, such as cocaine, for perinatal lead exposures (22), although further research is needed in this domain to determine the extent to which these results generalize to other rewarding stimuli following lead exposure.

Neuroimaging Findings

With the advent of neuroimaging techniques such as magnetic resonance imaging (MRI), researchers have also been able to better characterize the impact of lead exposure on human brain structure and function. Studies on adults with high childhood lead exposure found decreased gray matter volume and alteration to myelination and axonal integrity, suggesting altered white matter connectivity (23–25). Reductions in gray matter volume occurred in the anterior cingulate and ventrolateral prefrontal cortices in men and in the inferior parietal lobe in women (23). This effect of a global reduction in gray matter volume was replicated when associated with a proxy of lead risk exposure in a large, diverse sample of 9- to 10-year-old children from the Adolescent Brain Cognitive Development (ABCD) Study, although this study did not measure BLLs directly (26). More recently, evidence from a resting-state functional MRI study found that prenatal exposure to lead was related to different age-related fetal brain patterns, such that lead-exposed fetuses showed stronger age-related lateral to posterior cingulate functional connectivity and weaker functional connectivity between insular and temporal areas relative to lead-naive fetuses, suggesting early alteration in systems supporting higher-order cognitive and regulatory functions (27).

Impact on Mental Health

Exposure to heavy metals such as lead has been documented to have a substantive impact on the development of neurocognitive functions such as attention, memory, and general executive function (28–36) and has been reviewed elsewhere (29,37,38). Newer studies have expanded on these findings by exploring the impacts of lead exposure on mental health problems and developmental disabilities such as autism spectrum disorder (ASD) and learning disabilities (38). Both internalizing and externalizing behaviors have been reported to relate to lead exposure in children (39), as have schizophrenia (40) and childhood attention-deficit/hyperactivity disorder (ADHD) (21,37,41–47). More recent meta-analyses investigating the role of childhood lead exposure in increasing ADHD prevalence suggest an even more specific effect of lead on attention and response inhibition behaviors associated with ADHD (37). High levels of lead in red blood cells and lead urinary levels were also reported in at least 1 cohort study of children with ASD, although the design of the study did not allow for causal inferences in this relationship (48).

Overall, lead exposure has wide-ranging implications for a variety of neuropsychological processes that are often associated with mental health problems, particularly those associated with ADHD. Further research is needed to elucidate not only the particular pathways through which lead exposure results in mental health problems, but also the extent and magnitude of these effects, given recent calls to attention to the variability of these effects in verbal and performance tests [see (49,50) for a discussion within the context of lead-IQ relationships]. While legislative actions over the past few decades have greatly reduced the number of individuals affected by chronic lead exposure, it will take years of maintained efforts to eliminate the negative effects of lead, given that house dust and soil contaminated by remnants of lead paint continue to be the most common and persistent sources of lead exposure in children (51), thus highlighting a multidisciplinary concerted effort to combat the impact of heavy metals such as lead on mental health.

OUTDOOR AMBIENT PM

Relevance to Public Health

Outdoor air pollution is a mixture of gaseous and solid particles that includes components derived from both natural and anthropogenic sources. The largest proportion of the health impacts of outdoor air pollution are attributed to PM, which is defined by its aerodynamic diameter (PM_{10}, <10 μm; $PM_{2.5}$ <2.5 μm; ultrafine, $PM_{0.1}$, <0.1 μm) (52). Children are likely to be the most vulnerable to potential neurotoxic effects of PM because brain maturation continues through the third decade of life (53,54). A recent literature review in adults concluded that there is evidence to support the hypothesis of links between PM exposure and depression, anxiety, and suicide risk, but further reviews with a focus on children are needed (55). In addition, social stratification of exposure to outdoor PM is common; low socioeconomic areas and neighborhoods with a high percentage of racial/ethnic minorities (i.e., Black, Latinx, Native American, and Asian populations in the United States) are more likely to be exposed to higher levels of PM than predominantly White neighborhoods (56).

Sources of Exposure

Primary sources of outdoor PM—especially $PM_{2.5}$—vary by location and include traffic emissions, road dust, industrial processes, commercial cooking, agricultural processes, wildfires, and many other anthropogenic and natural sources (Figure 1; Table S1). Secondary PM is formed in the ambient atmosphere as gas-phase chemical compounds interact, form new particles, and condense onto existing particles (57).

Potential CNS Mechanisms

Mechanistically, outdoor ambient air pollution may affect the brain by acting either directly via transport of nanosized particles or secondarily through systemic changes leading to increased neuroinflammation and oxidative stress (58–60). At the neural level, exposure to small particles such as $PM_{2.5}$ and nanosized PM during development alters dendritic spine density (61) and neurogenesis (62) and affects microglial cells (59,63). These are important neuronal processes underlying synaptic proliferation and “pruning” and are essential hallmarks of childhood and adolescent neurodevelopment (60). Moreover, distinct neuronal cell types have different

biochemical sensitivity to oxidative stress, with key emotional regions, including the prefrontal cortex and amygdala, purported to be most susceptible (64). Finally, inhalation studies in animals have found that prenatal exposure to diesel exhaust alters neurotransmitter levels in various brain regions, including the amygdala (65,66).

Neuroimaging Findings

Similar to lead exposure, emerging cross-sectional human MRI findings suggest that prenatal and postnatal childhood $PM_{2.5}$ exposure may affect brain structure and function (67). Using anatomical MRI, prenatal $PM_{2.5}$ exposure has been linked to thinner gray matter cortices in the prefrontal and cuneus regions (68) and widespread smaller white matter surface area (69) and smaller corpus callosum volumes (70) in childhood. Beyond the prenatal period, childhood $PM_{2.5}$ exposure has been linked to altered cortical thickness in gray matter of the frontal, parietal, and temporal lobes and subcortical volumes in 9- to 10-year-old children from the ABCD Study (71). More recent work has shown associations between prenatal air pollutant exposure and white matter microstructural differences using diffusion MRI at ages 9 to 12 years (72), as well as associations between air pollution mixtures during childhood and altered brain activity during a sensory task and differences in functional connectivity of large-scaled brain networks, including the default mode network (73).

Impact on Mental Health

Prenatal and childhood air pollution exposure has been associated with poor neurodevelopmental and emotional outcomes (53,54,74,75), including emotional behavioral problems (76), impaired emotional regulation (77), anxiety/depression (76–81), ADHD symptoms (70,82,83), ASD (84,85), psychotic experience (86), and increased likelihood of being prescribed psychiatric medication (87). More research is needed to establish the strength of these associations and to determine which behavioral and mental health outcomes are most affected. However, considerable heterogeneity exists among associations observed in epidemiological studies, with some studies failing to observe these aforementioned associations between air pollution exposure and mental health problems (88,89). Inconclusive findings may stem from the inability to use identical methods of exposure assessment across development in heterogeneous cohorts of children (88,89). Furthermore, heterogeneity in the method of exposure assessment (spatial modeling, personal air monitors, etc.), limitations in study population size, variation in the lag time between exposure and outcome, and variation in exposure age contribute to ongoing uncertainty in establishing causal links between PM exposure and mental health outcomes in children.

Despite this, experimental animal studies have found that exposure to outdoor $PM_{2.5}$ and nanosized PM in utero as well as during childhood and adulthood may result in long-term behavioral consequences, including greater anxious and depressive-like symptoms (61,62,65,90–95). Additional studies have also found that prenatal exposure to diesel exhaust and early postnatal exposure to nanosized PM is associated with increased displays of aggression (65) and poor behavioral control (96,97) in mice.

In summary, emerging data suggest a link between outdoor PM and mental health. Further research is needed to clarify this link and to explore complex interactions with social stratification, outdoor air pollution, and mental health.

ENDOCRINE-DISRUPTING CHEMICALS

Relevance to Public Health

EDCs are defined by the World Health Organization as exogenous chemicals that interfere with the endocrine system and thus cause adverse effects in an organism, including developmental malformation, increased risk of cancer, reproductive problems, and interference with normal function of the immune and nervous systems (98–100).

Two scientific statements published by the Endocrine Society have sought to provide a comprehensive review of EDC-related literature, including an in-depth look at the effects of EDCs on neuroendocrine systems and neurophysiology (101,102).

Exposure to these compounds—especially during critical windows such as fetal development, childhood, and puberty—may lead to permanent defects that do not appear until later in life (100). At a population level, exposure to EDCs has been observed as consistently higher among low-income individuals and ethnic/racial minorities compared with higher-income White participants (103), contributing to a greater economic burden of EDC-related disease for Black and Latinx populations in the United States (104).

Associations have been explored between EDCs and a number of psychiatric neurodevelopmental disorders, including ASD, ADHD, anxiety and stress disorders, depression, and others (105). Given that more than 800 chemicals are known or suspected to have endocrine-disrupting properties, a comprehensive discussion of associations between EDCs and mental health outcomes is outside the scope of this article (99,100,106). This article will focus on 3 types of EDCs—bisphenol A (BPA), phthalates, and polychlorinated biphenyl compounds (PCBs)—that are repeatedly identified in literature as disrupters of neurodevelopment.

Sources of Exposure

BPA is ubiquitous in the environment, and more than 90% of children in multiple regions around the world have confirmed exposure (107–111). BPA is commonly found in reusable bottles, microwave ovenware, food storage containers, the internal coatings of food and beverage cans, and children's toys; exposure occurs through ingestion and dermal absorption (Figure 1) (112,113). Phthalates are a family of EDCs that are divided into two subgroups with distinct commercial uses and toxicological properties (114,115). Low molecular weight phthalates are used in pharmaceuticals, cosmetics, personal care products, and packaging (Figure 1) (114,116). Owing to their molecular structure and lack of covalent bonds within the polymer matrix, these chemicals easily leach from products into the environment, and human exposure occurs through food ingestion, dermal absorption, and inhalation (114,116). Finally, PCBs are synthetic organochlorine compounds that were banned in many countries, including the United States, in the 1970s, but they are still persistent and ubiquitous

environmental contaminants (117–119). They were popular for multiple industrial uses in the early 1930s, including as capacitor and transformer oils, hydraulic fluids, lubricating oils, and plasticizers (Figure 1; Table S1) (119).

Potential CNS Mechanisms

EDCs do not necessarily lead to direct neurotoxic damage (i.e., poisoning neural tissue and causing cell death). Instead, they are capable of disrupting the structure and function of neural systems indirectly via neuroendocrine-related mechanisms (120). There are 2 major pathways by which EDCs may affect the brain: by disrupting neuroendocrine processes originating in the hypothalamus and/or by acting on steroid hormone receptors and signaling pathways throughout the brain (101). The developing human brain is especially vulnerable to EDCs during fetal development, during which these chemicals can impair critical development steps, including neurogenesis, neuronal migration, neuronal and glial cell differentiation, myelination, and synaptogenesis (120–122). Many EDCs can cross the placenta and enter the fetal bloodstream, where they may interact with steroid and xenobiotic receptors, impacting estrogen signaling, interfering with hormone transport, binding hormone receptors, and disrupting hormone synthesis (105,121,123,124).

The specific mechanisms by which EDCs may affect neurobehavioral development have been explored in depth elsewhere (99,101,120). Phthalate, PCB, and BPA exposure have all been associated with thyroid homeostasis interference and decreased thyroid maternal hormone levels. Maternal hypothyroxinemia—a state of low free maternal thyroid hormones—during the prenatal period has been associated with delayed cognitive and neuromotor development and increased ADHD symptoms in children (102,105,125–129). Research has suggested that the estrogen-mimicking capabilities of BPA make it capable of dysregulating endocrine signaling pathways during the perinatal period (105). Similarly, it has been proposed that some of the possible behavioral effects of BPA—especially those related to anxiety and depression—occur through its estrogenic activity, including its ability to bind to estrogen receptor subtypes, which are located in brain regions critical for stress response (105). In animal studies, associations between EDCs and mental health outcomes vary in strength, direction, and magnitude and depend on multiple factors, including species, dose, exposure timing, and outcome measurement (101). Yet, there is consensus that the expression of genes and proteins related to steroid hormone receptors in the brain are highly sensitive to EDC exposure, especially during critical windows of brain development (101).

Neuroimaging Findings

Emerging evidence suggests that prenatal exposure to phthalates, in particular, may be related to MRI brain morphometry and connectivity in adolescence. A study measuring maternal concentrations of phthalate esters during the third trimester was associated with reduced anterior cingulate and cerebellum volumes in adolescents and with reduced diffusion in white matter tracts in the corpus callosum, corona radiata, superior fronto-occipital fasciculus, and superior longitudinal fasciculus (130). Another study recruiting mother–child pairs found significant relationships between prenatal phthalate concentrations and regional brain activity at rest, with higher exposure related to differences in connectivity patterns seen for superior and middle frontal, middle and inferior temporal, anterior cingulum, and insular brain regions in female adolescents (131).

Impact on Mental Health

BPA has been linked to anxiety and hyperactivity in children, with some studies detecting disproportionate effects in boys (132–134) or girls (135,136). These studies collected maternal urinary samples during the prenatal period and evaluated anxiety symptoms and scores at 2 years of age (136) and at 10 and 12 years of age (137). Results varied by exposure window, suggesting different critical windows of exposure during fetal development for boys and girls (105). Similar links have been established between prenatal and early-life exposure to BPA and symptoms of depression, anxiety, and increased aggressive behavior during childhood and adolescence, with particular susceptibility noted in males (133,134,137,138). Animal studies have supported these findings, showing associations between prenatal BPA exposure and increased aggression and changes in the dopaminergic system in the limbic forebrain (136). Although these studies support potential associations between pre- and perinatal exposure to BPA and behavioral measures that suggest behavioral problems, BPA has not been definitively linked to diagnosis of any disorders.

Multiple epidemiological studies have detected associations—sometimes with sex-specific effects—between prenatal exposure to phthalates and increased behavioral problems in childhood (139–143). In a 2010 study, prenatal low molecular weight phthalate metabolites were associated with elevated aggression, attention problems, conduct problems, depression, and higher scores on an Externalizing Problems Composite score and the Behavioral Symptom Index (139). Similarly, a 2017 study using subscores from the Strength and Difficulties Questionnaire detected associations between the presence of two phthalate metabolites in maternal cord blood and internalizing behavior, relationship problems, and emotional symptoms in 3-year-old boys (100).

Multiple studies exist linking chronic exposure to low doses of PCBs to lower child cognition and other neuropsychological outcomes (119,144). Two 2010 studies detected significant associations between low-level prenatal exposure and behavioral outcomes in young children, including increased inattention in 11-month-old infants (118) and an increased state of unhappiness and anxiety during testing sessions in 5-year-olds (125). Finally, a 2003 Michigan study found associations between prenatal PCB exposure and greater impulsivity, poorer concentration, and poorer working memory in 11-year-old children (117); such symptoms are sometimes, but not always, impaired in individuals with ADHD (37).

Together, the literature suggests that there is concern that early-life exposure to EDCs may influence mental health difficulties in children. Additional neighborhood-level stressors may interact with EDC exposure and impact associations between EDCs and mental health outcomes (145,146). Further research is needed to confirm associations between EDCs and

mental health outcomes and to investigate how disparities in exposure to EDCs may further impact risk.

CONCLUSIONS

While urban life may confer several benefits, it may be accompanied by numerous exposures that may be harmful or unsafe for the CNS. Exposure to heavy metals such as lead, outdoor air pollution, and EDCs may affect neuropsychological factors, particularly when these negative exposures occur at an early age, either in utero or in early childhood. While a number of effects and candidate mechanisms have been discussed here, for many neurotoxicants it is difficult to establish causality between a single bad actor and diagnosable disorders in human epidemiological studies, owing to limits in sample size, interindividual variations in risk factors, gene-by-environment interactions, and the complex mixtures of exposures that different people experience (147). Furthermore, despite emerging evidence from epidemiological and animal model studies that suggest associations between neurotoxicants, such as metals, air pollution, and EDCs, and neural and behavioral outcomes, it can take years for causality to be widely accepted (120). Despite this (perhaps dismal) landscape, it is important to state the importance of awareness and advocacy surrounding the issue of neurotoxicant exposures in order to influence policy makers that can enact legislation to largely mitigate and eliminate these toxic environmental exposures. It is also important to leverage and highlight the efforts of environmental justice activists and community organizers, usually from historically marginalized communities, bringing attention to how these neurotoxicants disproportionately impact their communities. Mitigating and eliminating the negative effect of neurotoxicant exposures requires a multifaceted approach. Further research is needed that can explore mechanisms taking into account the complex dynamics in which environmental, social, and political factors occur (5), as well as elucidate how both the timing and accumulation of neurotoxicants impact the CNS and subsequent risk for the development of mental health problems.

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