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Environmental Mechanisms of Neurodevelopmental Toxicity

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Abstract

Purpose of Review—With the incidence of neurodevelopmental disorders on the rise, it is imperative to identify and understand the mechanisms by which environmental contaminants can impact the developing brain and heighten risk. Here, we report on recent findings regarding novel mechanisms of developmental neurotoxicity and highlight chemicals of concern, beyond traditionally defined neurotoxins.

Recent Findings—The perinatal window represents a critical and extremely vulnerable period of time during which chemical insult can alter the morphological and functional trajectory of the developing brain. Numerous chemical classes have been associated with alterations in neurodevelopment including metals, solvents, pesticides, and, more recently, endocrine-disrupting compounds. Although mechanisms of neurotoxicity have traditionally been identified as pathways leading to neuronal cell death, neuropathology, or severe neural injury, recent research highlights alternative mechanisms that result in more subtle but consequential changes in the brain and behavior. These emerging areas of interest include neuroendocrine and immune disruption, as well as indirect toxicity via actions on other organs such as the gut and placenta.

Summary—Understanding of the myriad ways in which the developing brain is vulnerable to chemical exposures has grown tremendously over the past decade. Further progress and implementation in risk assessment is critical to reducing risk of neurodevelopmental disorders.

Keywords

Neurodevelopment; Neurotoxicity; Xenobiotic; Neuroendocrine; Neuroimmune

Introduction

Neurodevelopment begins as early as three weeks into gestation and continues through the neonatal period and puberty, and, to some extent even spans into adulthood. The perinatal period, in particular, embodies a unique window of susceptibility during which the

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Compliance with Ethical Standards

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rudimentary structures of the central nervous system (CNS) are formed and organized. During this phase, intricate and coordinated signaling events control complex processes such as cell proliferation, differentiation, migration, apoptosis, and synaptic pruning [1–3]. Such developmental plasticity is necessary for proper brain development but also leaves the brain vulnerable to perturbation, as it is highly responsive to both intrinsic and extrinsic stimuli [4–6]. Therefore, exposure to environmental insults, such as exogenous chemicals, during these sensitive developmental periods can result in unwanted long-term or permanent changes in brain form and function [7•, 8]. Because of the profound and rapid change that occurs during this time, the gestational and neonatal periods are critical windows of intense focus for understanding how and to what degree exposure to contaminants can lead to permanent and life-long impacts on the brain and behavior [9, 10].

Involuntary exposure to environmental toxicants can occur through inhalation, ingestion, and dermal contact with contaminated air, food, water, house dust, and soil [7•]. The developing fetus or newborn frequently experiences higher exposure levels than adults for several reasons. First, the fetus and neonate are not as well protected as once believed, as many contaminants have been shown to reach the fetus through placental transfer [11•] or the developing newborn in breast milk [12, 13]. Second, the metabolic enzymes responsible for detoxifying exogenous chemicals and the blood brain barrier are not yet at their full functional capacities [8, 14••, 15–18]. Energy demands are also much higher during development. Therefore, relative to their body weight, the very young have higher respiration rates and food consumption, which can lead to higher exposures. Additionally, babies and young children participate in behaviors that increase their contact with contaminated media, including crawling and frequent hand-to-mouth behaviors [7•, 9, 19]. With such a high degree of vulnerability, due to uniquely high levels of exposure and the extremely plastic nature of the developing brain, it is imperative to understand how and what chemicals can impact the developing brain in order to curtail risk of neurodevelopmental disease.

Approximately 10–15% of infants born in the USA are impacted by neurodevelopmental disorders [20], which include impairments in the growth and development of the brain, leading to disabilities in learning, memory, and emotion. With the incidence of these ailments on the rise [21], it has become increasingly important to identify and understand the mechanisms by which changes to the perinatal environment influences risk. Although genetic factors clearly contribute to these non-communicable disorders, the rapid rate of increase signifies that some other, likely environmental, influences are also involved [13, 21, 22]. These include quality of parental care, nutrition, socioeconomic status, and other cultural factors, but also undoubtedly, pollution [13, 23, 24].

With greater than 80,000 chemicals registered with the US Environmental Protection Agency (EPA) for commercial use, only a small fraction have been studied for their potential neurotoxic properties [13, 25]. Although counts differ across studies, about 200 chemicals are currently characterized as neurotoxic to humans [13, 26]. Even less is known about which of these chemicals are *developmentally* neurotoxic, and none have been systematically screened for such properties before entering commercial use [27]. Accumulating epidemiological and experimental research has linked exposure to several

neurotoxic environmental contaminants including lead, mercury, air pollution, and a variety of pesticides and flame retardants with adverse consequences on brain development and heightened risk of neurodevelopmental disease [7•, 19, 28••]. In this review, we will focus on evidence of xenobiotic-related mechanisms by which neurodevelopmental damage may arise.

Defining Developmental Neurotoxicity

Neurotoxicity is defined by the US EPA as an adverse change in structure and/or function of the central nervous system and/or peripheral nervous system measured at the neurochemical, behavioral, neurophysiological, or anatomical levels [19, 29]. Classically, this culminates in cell death and a degree of quantifiable pathology. Examples of well-characterized neurotoxins include lead, mercury, and organophosphate (OP) pesticides such as chlorpyrifos (CPF) [13, 14]. Endocrine-disrupting chemicals (EDCs) were identified and defined nearly 30 years ago, and have rapidly become of great concern for their potential to impact the brain and behavior [30, 31]. EDCs, characterized as natural or synthetic chemicals that can interact with any aspect of hormonal systems [31, 32••], do not fit in the classical definition of neurotoxicant in that they do not typically result in overt cell death and neural pathology, but can have subtle but profound effects on development, physiology, and behavior [33]. Similarly, neuroendocrine disruption has been described as alterations in the structure or function of the neuroendocrine system resulting from exposure to an exogenous chemical or mixture [30]. For this review, “neurotoxicant” will be used as an inclusive term defining any chemical that can impact the developing brain and/or induce behavioral effects regardless of mechanism.

The majority of chemicals recognized as neurotoxic generally fall into one of three broad groups, metals, solvents, and pesticides [13]. Historically, the primary method of identifying these neurotoxins has been linking high-dose, often unintentional or occupational, exposures with clinical symptoms and/or obvious pathologies in humans [13]. More recently, a suite of tools including in silico, animal and cell-based models, has expanded the capacity to identify risk and possible mechanisms of action at much lower, environmentally relevant, levels of exposure. A classic example is lead (Pb) poisoning, which can lead to severe disability and death in the case of high-dose exposure at any age, or significant behavioral and learning disabilities following early life, low-dose exposure [13, 14]. Significantly, epidemiologic research has revealed associations between Pb exposure and reduced intelligence in children [13, 34–36] at doses that do not produce clinical symptoms in adults. This highlights the importance of critical periods of sensitivity, but also the recognition that chemicals can impact the brain via multiple mechanisms. In the case of Pb, these mechanisms include oxidative stress and altered neurotransmitter systems, and two more recently described modes of action: neuroendocrine and immune system disruption (Table 1).

Mechanisms of Developmental Neurotoxicity

Oxidative Stress

Reactive oxygen species (ROS), such as superoxide anions and hydroxyl radicals, can form through multiple mechanisms in the brain, including induction of mitochondrial dysfunction, redox cycling, and enzymatic bioactivation of substrates. These processes occur under normal conditions and are even necessary for normal cell function. However, these processes can become pathological when the balance between the production and detoxification of ROS is shifted [53]. Epidemiology studies as well as postmortem human brain proteomic, transcriptomic, and metabolomic studies have revealed a strong association between oxidative stress and neurotoxicity/altered neurodevelopment [7•]. Exposure to xenobiotics can lead to an abnormal buildup of ROS, which are then able to interact with and damage macromolecules, such as DNA, RNA, lipids, and proteins [54]. Ultimately, this can disrupt processes such as gene expression and signal transduction which, consequently, impedes normal neurodevelopmental processes.

The brain is particularly vulnerable to oxidative stress because it is high in polyunsaturated fatty acids, which are easily oxidized and has naturally high oxygen requirements. During development, this susceptibility is even greater since the developing brain has a low level of antioxidant enzymes and an even higher rate of oxygen consumption [55–57]. Oxidative stress is the textbook mechanism of neurotoxicity, classically defined, because chemically induced oxidative stress frequently leads to neuronal cell death. Halogenated insecticides, such as permethrin and dichlorvos, are prime examples of chemicals that can disrupt ROS homeostasis and induce deleterious apoptosis [58–60]. Oxidative damage has also been observed, in the developing brain, following exposure to the OP pesticide CPF [41]. A large number of other environmental contaminants with other, sometimes more well characterized, modes of action have also been shown to induce oxidative stress including Pb and bisphenol A (BPA) [7•]. Biochemical and molecular changes associated with ROS-mediated oxidative stress following exposure to arsenic include reduced activity of mitochondrial complexes, decreased protein synthesis, lipid peroxidation, and altered membrane fluidity [61]. PCBs, which can induce oxidative stress, can also alter neurotransmitter systems, and are considered a classic example of an EDC. For these and other chemicals, the overt toxicity induced by oxidative stress could be an underlying factor for other consequential effects including impaired neurotransmitter and neuroendocrine signaling and inflammation. Therefore, oxidative stress may be a key component of neurotoxicity mechanisms.

Altered Neurotransmitter Systems

Early in embryonic and fetal development, prior to synaptic development, neurotransmitters regulate numerous neurodevelopmental processes. Disruption of these neurotransmitter systems has been associated with a variety of neurodevelopmental disorders. Example relationships include reduced dopamine (DA) and attention-deficit hyperactivity disorder (ADHD), or hyperserotonemia and autism spectrum disorder (ASD) [7•]. Therefore, disruption of neurotransmitter systems during brain development could result in significant, long-term deficits in brain structure and function. One classic example of neurotransmitter disruption is “cholinergic syndrome” which results from exposure to OP pesticides such as

malathion, parathion, and CPF. In the same family as the notorious nerve agents sarin and cyclosarin, OP pesticides inhibit the enzyme acetylcholinesterase, resulting in excitotoxicity as a result of CNS overstimulation due to prolonged stimulation by acetylcholine. Adverse neurological symptoms include headache, dizziness, confusion, blurred vision, slurred speech, and death [62]. Prolonged low-dose exposure heightens risk of cardiovascular and respiratory disease, cancer, and premature birth. These chemicals can also perturb other neurotransmitter systems. For example, CPF can alter serotonin (5-HT) signaling. Developmental exposure to CPF has been found to impact 5-HT, not by altering its degradation, but by increasing its reuptake and the expression of 5-HT receptors, altering 5-HTergic synaptic function. Finally, these CPF-induced alterations have been associated with changes in 5-HT-dependent behaviors, such as learning and memory [63–66].

Pyrethroids are now the most commonly used insecticides in US homes, and exposure has been associated with altered behavioral phenotypes, such as locomotor activity impairments, impulsivity, and memory deficits [67–69]. The dopaminergic system has been identified as a potential target of pyrethroid toxicity. Exposure to the pyrethroid deltamethrin has been shown to result in increased uptake and release of DA [70], increased expression of DA transporter (DAT) [69, 71, 72], and reduced expression of DA receptors [73]. DA cell death in the substantia nigra ultimately culminates in Parkinson's disease, a disorder now well recognized to result from a combination of biological and environmental factors [74]. More common in men than women and strongly associated with proximity to agriculturally intense regions, heightened Parkinson's disease risk is linked with several insecticides including rotenone, permethrin, and organochlorine herbicides such as 2,4-D. The latter is of particular concern now that the EPA has approved the use of 2,4-D resistant genetically modified crops in the USA, thereby all but guaranteeing increased and widespread exposure via contaminated food[75]. These examples highlight the exquisite sensitivity of neurotransmitter systems to environmental chemicals and also the diverse suite of detrimental outcomes of disruption on neurodevelopment and brain aging.

Neuroendocrine Disruption

The organization of neural networks relies immensely on hormonal signaling. Numerous hormones, particularly steroid hormones, play critical roles in brain cell differentiation, migration, synaptogenesis, and sex-specific organization of neural networks [33, 76–81]. They are therefore vulnerable to endocrine disruption and EDCs. The most well-characterized mechanisms of developmental neuroendocrine disruption involve a region of the brain known as the hypothalamus [82•], with impacts on reproductive physiology and behavior as the primary endpoints of concern [83]. The bulk of neuroendocrine disruption research has focused on disrupted estrogen, androgen, and thyroid hormone signaling at various levels of the hypothalamic-pituitary-gonadal (HPG) axis and hypothalamic-pituitary-thyroid (HPT) axis. Decades of work has revealed that exposure to chemicals that target the HPG and HPT axes can have significant impacts on the brain and behavior, such as changes in sexually dimorphic brain morphology, masculinization/feminization of neuroendocrine pathways, and alterations in both reproductive and non-reproductive behaviors [30, 47, 81, 82•, 84–87]. Neuroendocrine disruption can also occur outside the hypothalamus and to other hormone systems including peptide hormones such as GnRH, insulin, oxytocin (OT),

vasopressin (AVP), and kisspeptin. For example, exposure to atrazine, a commonly used herbicide, has been found to inhibit the preovulatory leutinizing hormone (LH) surge and pulsatile release associated with reduced GnRH neuronal activity [88–90]. OT and AVP have been found to be susceptible to perinatal BPA and methoxychlor exposure, with observed changes in the number of OT and AVP neurons and disruption of associated behaviors [91, 92].

Significant progress has been made identifying potential mechanisms of endocrine disruption and, similarly, developmental neuroendocrine disruption, including changes in steroid metabolism and biosynthesis, receptor degradation, DNA methylation, and direct and indirect effects on steroid receptor activity [33, 93]. For example, exposure to well-known EDCs, such as PCBs and BPA, has been shown to alter circulating hormone levels [94–97], gene expression [82, 98–105], and nuclei volume in sexually dimorphic brain regions [106, 107]. In humans, developmental neuroendocrine disruption by these chemicals and others such as dichlorodiphenyltrichloroethane (DDT) and tributyltin (TBT) has been linked with cognitive deficits, obesity and metabolic syndrome, loss of behavioral sex differences, impaired fertility and reproductive function, and behavioral deficits [31, 32••].

Although the hypothalamus has been the primary brain region of EDC research focus, there is also evidence that EDCs can impact extra-hypothalamic regions of the brain, such as the hippocampus. The hippocampus plays an important role in learning and memory, and its organization is regulated by estrogen, androgen, and thyroid hormones [82•, 108]. Developmental processes, like neurogenesis and synaptogenesis, have been shown to be particularly susceptible to EDCs in the hippocampus. For example, exposure to BPA over the perinatal period has been shown to reduce synaptic density and maturation in the CA1 region of the hippocampus, possibly as a result of changes in the expression of synaptic proteins and glutamate receptors [109]. There is also evidence for developmental neuroendocrine disruption in other hormone-sensitive regions including the amygdala, cortex, and cerebellum [82•]. However, more work is needed to further understand the vulnerability of underappreciated brain regions to EDCs, and the functional consequences of EDC-related changes to these regions.

Disruption of the stress axis, which encompasses the hypothalamic-pituitary-adrenal (HPA) axis, by EDCs and environmental contaminants has not received as much attention as the HPG and HPT axes. However, compelling evidence indicates that stress can have significant impacts on the developing brain. The adolescent brain is particularly vulnerable to stress, resulting in changes in brain organization and structure such as altered dendritic pruning, changes in hippocampal volume and function [110, 111], reductions in learning and memory, depression, and increased participation in risky behaviors such as smoking, unprotected sex, and drug use [112]. In the perinatal period, the HPA axis has been shown to be sensitive to changes in maternal stress and circulating corticosterone (CORT) levels [113–115], with males being possibly more vulnerable than females [116]. There is some evidence that developmental exposure to PCBs can impact the HPA axis, with reductions in corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH), and circulating levels of CORT, in juveniles and adults [117–119]. BPA has also been shown to have the potential to interact with and disrupt the HPA axis. Perinatal exposure to BPA alters

CORT and ACTH secretion, and induces changes in the expression of CRH and glucocorticoid receptor mRNA in the adult rat brain [120].

Overall, our understanding of the neuroendocrine mechanisms by which exposure to environmental contaminants, and in particular EDCs, can impact the developing brain has seen a lot of recent progress. However, more work is needed to better understand mechanisms outside of estrogen, androgen, and thyroid hormone signaling, and functional repercussions of alterations in extra-hypothalamic regions of the brain.

Immune System Disruption

The immune system is inextricably linked with the CNS and plays a critical role in brain development and function [121]. With evidence of linkages between inflammation and neural disorders rapidly growing, neuroimmune disruption has become a hot topic in developmental neurotoxicity [122, 123]. Resident immune cells, such as microglia, along with astrocytes, produce inflammatory molecules, including cytokines and chemokines, in response to injury or infection, but these cells and their signaling molecules are also present under homeostatic conditions [124, 125]. Classically, glia have been characterized as the support cells for neurons but their role is far more complex. For example, astrocytes are neuroprotective via maintenance activities such as buffering ion levels, regulating water balance, and modulating synaptic activity, but also produce anti-inflammatory cytokines and neurotrophins. Glia and cytokines have been shown to partake in complex developmental processes, such as apoptosis, axonal growth, formation and maintenance of synapses, and glial cell migration and differentiation [126–130]. Astrocyte-microglial interactions are essential to maintain innate CNS immunity although much remains to be understood about the nature of that relationship, particularly during development. Exposure to infectious agents and subsequent activation of either the maternal or fetal immune system has been associated with alterations in fetal brain development and increased risk of neurodevelopmental disorders including ASD [131–134]. Therefore, perturbations of the immune system during critical windows of brain development could lead to abnormal brain structure and function.

There is rapidly compounding evidence that a variety of environmental contaminants can provoke an innate immune response and/or alter its trajectory. Several groups have hypothesized that environmental insults may impact the developing immune system, and result in long-term effects on brain function by impacting normal colonization of the developing brain by glial cell populations [125, 135, 136]. Microglia are derived from the yolk sac and take up residence in the CNS very early in development, and have therefore become of particular interest in the context of immune disruption and brain development [130]. It has previously been established that microglia are hormone sensitive [137–139], indicating they may be vulnerable to perturbation by EDCs. Changes in sex-specific colonization of the brain by microglia have been observed as a result of developmental exposure to BPA [48, 140•]. Although the functional significance of these findings remains to be determined, other studies have shown that changes in microglia colonization can impact synaptic remodeling [141]. Changes in signaling molecules produced by resident immune cells have been observed in the absence of activated microglia [142, 143],

suggesting that other cells that produce cytokines could be responsible for the observed changes in immune response. Other glial cell populations that are potential targets include astrocytes, oligodendrocytes, and NG2 (oligodendrocyte progenitor) cells. Similar to microglia, these glial cell types are hormone sensitive [144, 145] and therefore warrant further investigation, as they may also be vulnerable to perturbation by EDCs.

Numerous proinflammatory cytokines participate in immune function; however, only a handful are believed to play a particularly critical role in the brain. These include IL-1 β , IL-6, and TNF α . Upregulation of these inflammatory signals has been observed in the hypothalamus, dentate gyrus of the hippocampus, and amygdala following immune challenge and may be associated with an increased risk for mood disorders [146]. Similar to changes in microglial colonization, the majority of studies assessing alterations in cytokines in the developing brain use approaches that model infection such as lipopolysaccharide (LPS) injections. These studies have provided a critical foundation from which effects related to exogenous chemicals can be compared, and crucial evidence showing that activation of the maternal immune system can alter fetal brain cytokines [143, 147]. Various exogenous chemicals, such as phenols (e.g., BPA) and pesticides (e.g., CPF), have been shown to disrupt immune cells and the cytokines they produce [148, 149], including during stages of development [150, 151], with both increases and decreases in inflammatory markers observed. There is some evidence of altered neuroimmune response following exposure to exogenous chemicals; however, we are just beginning to further elucidate these mechanisms and assess other immune-related signaling molecules, such as chemokines. Although there is a lot of interest in how disruption of the immune system can impact the developing brain, more work is needed to understand how chemical exposures stimulate an immune response in the developing brain.

Indirect Toxicity

Neurotoxicity can also occur via insult outside of the brain itself. The brain is linked to and influenced by many other organs and organ systems in the body, such as the liver, kidneys, pancreas, and gastrointestinal tract. Communication within the “brain-gut axis” for example is now recognized to influence body weight, sleep, and risk of mood-related disorders [152, 153]. Consequently, there is growing interest in how disruption to the gut microbiome and inflammation of peripheral tissues including the gastrointestinal tract might impact brain development and behavior.

The placenta is the site of nutrient exchange between mother and fetus, but it also provides critical support of fetal growth through hormone and neurotransmitter production. Not surprisingly, the placenta has been found to play a unique and critical role in neurodevelopment and dysfunction of the placenta can impact neurodevelopment [11, 154]. There are several examples of stress-induced inflammation leading to placental dysfunction and altered neurodevelopment [155, 156]; however, almost no studies have tested whether this type of response can occur from exposure to exogenous chemicals. Furthermore, although the placenta is meant to provide some protection for the fetus, a variety of environmental contaminants, including heavy metals, OPs, and flame retardants, have been shown to reach the fetus by passing through the placenta [157, 158]. Growing evidence that

contaminants can accumulate in placental tissue [159–163] emphasizes the possibility that the fetus may experience greater exposures than the mother. Therefore, during the gestational window, neurodevelopment can be impacted by direct toxicity to the developing brain, but also, indirectly, via direct toxicity to the placenta, leading to disrupted placental signaling factors critical for brain development including neurotransmitters and hormones. These are two examples of novel targets of xenobiotics that may contribute to neurotoxic effects of developmental exposures and thus warrant further investigation.

Conclusions

There is a significant amount of evidence from experimental and epidemiological studies indicating that developmental exposure to environmental contaminants can profoundly impact neurodevelopmental endpoints and contribute to neurodevelopmental disease risk. Because of the dynamic nature of brain development, it is imperative to recognize that exposure-related outcomes depend on the developmental exposure window, and that effects observed in children may not be observed in adults or only at much higher dose levels. More research is needed to understand the possibly unique vulnerabilities of the adolescent brain, and the myriad of exposures this population experiences.

The number of chemical classes identified as neurotoxic is alarming because it only continues to grow as more is understood about how the brain is vulnerable to chemical insult, and our regulatory system continues to fail to remedy known high-risk chemicals, such as CPF, and replaces compounds, such as BPA, with alternatives for which we lack toxicity data but appear to be structurally and toxicologically similar (such as BPS and other bisphenol analogs). The situation is further complicated by the reality of multiple exposure routes and continuous exposure to complex mixtures. Many neurotoxic chemicals have the potential to elicit their effects through multiple modes of action (Table 1), and these modes of action are likely to overlap. The endocrine system has been shown to interact with the immune system, by mediating gene transcription of proinflammatory cytokines for example, and mediators of the innate immune system can feedback on the brain and regulate endocrine signaling [164]. Finally, although we have made a great deal of progress in understanding the mechanisms by which chemical insult directly impacts the developing brain, it is critical for future efforts to take a more systems approach and consider the possibility that neurotoxicity might result from actions on other organs such as the placenta. Disruption of these relationships may represent a potentially critical but underappreciated route of disrupted brain organization.

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References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

•• Of major importance

1. Adinolfi M The development of the human blood-CSF-brain barrier. *Dev Med Child Neurol* 1985;27(4):532–7. [PubMed: 4029526]
2. Rodier PM. Vulnerable periods and processes during central nervous system development. *Environ Health Perspect* 1994;102(Suppl 2):121–4. 10.1289/ehp.94102121.
3. Bayer SA, Altman J, Russo RJ, Zhang X. Timetables of neurogenesis in the human brain based on experimentally determined patterns in the rat. *Neurotoxicology*. 1993;14(1):83–144. [PubMed: 8361683]
4. Meredith RM. Sensitive and critical periods during neurotypical and aberrant neurodevelopment: a framework for neurodevelopmental disorders. *Neurosci Biobehav Rev* 2015;50:180–8. 10.1016/j.neubiorev.2014.12.001. [PubMed: 25496903]
5. Kroon T, Sierksma MC, Meredith RM. Investigating mechanisms underlying neurodevelopmental phenotypes of autistic and intellectual disability disorders: a perspective. *Front Syst Neurosci* 2013;7:75 10.3389/fnsys.2013.00075. [PubMed: 24198768]
6. Marco EM, Macri S, Laviola G. Critical age windows for neurodevelopmental psychiatric disorders: evidence from animal models. *Neurotox Res* 2011;19(2):286–307. 10.1007/s12640-010-9205-z. [PubMed: 20607469]
7. Heyer DB, Meredith RM. Environmental toxicology: sensitive periods of development and neurodevelopmental disorders. *Neurotoxicology*. 2017;58:23–41. 10.1016/j.neuro.2016.10.017. [PubMed: 27825840] Overview of developmental periods of susceptibility to environmental toxicants and neurodevelopmental disorders and the common pathophysiological mechanisms of neurotoxicants.
8. Rodier PM. Developing brain as a target of toxicity. *Environ Health Perspect* 1995;103(Suppl 6):73–6. 10.1289/ehp.95103s673.
9. Koger SM, Schettler T, Weiss B. Environmental toxicants and developmental disabilities: a challenge for psychologists. *Am Psychol* 2005;60(3):243–55. 10.1037/0003-066X.60.3.243. [PubMed: 15796678]
10. Rauh VA, Margolis AE. Research review: environmental exposures, neurodevelopment, and child mental health—new paradigms for the study of brain and behavioral effects. *J Child Psychol Psychiatry*. 2016;57(7):775–93. 10.1111/jcpp.12537. [PubMed: 26987761]
11. Konkel L Lasting impact of an ephemeral organ: the role of the placenta in fetal programming. *Environ Health Perspect* 2016;124(7):A124–9. 10.1289/ehp.124-A124. [PubMed: 27479992] Critical summary of the role the placenta plays in regulating the fetal environment and how molecular changes in the placenta may contribute to aspects of fetal programming.
12. Weiss B, Amler S, Amler RW. Pesticides. *Pediatrics*. 2004;113(4 Suppl):1030–6. [PubMed: 15060196]
13. Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet*. 2006;368(9553):2167–78. 10.1016/S0140-6736(06)69665-7. [PubMed: 17174709]
14. Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. *Lancet neurology*. 2014;13(3):330–8. 10.1016/S1474-4422(13)70278-3. [PubMed: 24556010] A critical follow-up to their landmark 2006 paper and an overview of newly recognised and suspected developmental neurotoxicants with an emphasis on the probability of developmental exposure to unrecognised toxic chemicals.
15. Risau W, Wolburg H. Development of the blood-brain barrier. *Trends Neurosci* 1990;13(5):174–8. 10.1016/0166-2236(90)90043-A. [PubMed: 1693235]
16. Cole TB, Jampsa RL, Walter BJ, Arndt TL, Richter RJ, Shih DM, et al. Expression of human paraoxonase (PON1) during development. *Pharmacogenetics*. 2003;13(6):357–64. 10.1097/01.fpc.0000054092.48725.30. [PubMed: 12777966]
17. Mortensen SR, Chanda SM, Hooper MJ, Padilla S. Maturation differences in chlorpyrifos-oxonase activity may contribute to age-related sensitivity to chlorpyrifos. *J Biochem Toxicol* 1996;11(6): 279–87. 10.1002/(SICI)1522-7146(1996)11:6<279::AID-JBT3>3.0.CO;2-H. [PubMed: 9265078]

18. Benke GM, Murphy SD. The influence of age on the toxicity and metabolism of methyl parathion and parathion in male and female rats. *Toxicol Appl Pharmacol* 1975;31(2):254–69. 10.1016/0041-008X(75)90161-1. [PubMed: 1129797]
19. Tamm C, Ceccatelli S. Mechanistic insight into neurotoxicity induced by developmental insults. *Biochem Biophys Res Commun*. 2017;482(3):408–18. 10.1016/j.bbrc.2016.10.087. [PubMed: 28212724]
20. Bloom B, Cohen RA, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2008. *Vital Health Stat* 2009;10(244):1–81.
21. Rohlman DS, Anger WK, Lein PJ. Correlating neurobehavioral performance with biomarkers of organophosphorous pesticide exposure. *Neurotoxicology*. 2011;32(2):268–76. 10.1016/j.neuro.2010.12.008. [PubMed: 21182866]
22. Costa LG, de Laat R, Tagliaferri S, Pellacani C. A mechanistic view of polybrominated diphenyl ether (PBDE) developmental neurotoxicity. *Toxicol Lett* 2014;230(2):282–94. 10.1016/j.toxlet.2013.11.011. [PubMed: 24270005]
23. Hackman DA, Farah MJ, Meaney MJ. Socioeconomic status and the brain: mechanistic insights from human and animal research. *Nat Rev Neurosci* 2010;11(9):651–9. 10.1038/nrn2897. [PubMed: 20725096]
24. Suades-Gonzalez E, Gascon M, Guxens M, Sunyer J. Air pollution and neuropsychological development: a review of the latest evidence. *Endocrinology*. 2015;156(10):3473–82. 10.1210/en.2015-1403. [PubMed: 26241071]
25. U.S. Environmental Protection Agency. Chemical Hazard Data Availability Study: what do we really know about the safety of high production volume chemicals? 1998.
26. USGAO. Chemical regulation: options for enhancing the effectiveness of the Toxic Substances Control Act. U.S. Governmental Accounting Office; 2009.
27. Kalkbrenner AE, Schmidt RJ, Penlesky AC. Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence. *Curr Probl Pediatr Adolesc Health Care*. 2014;44(10):277–318. 10.1016/j.cppeds.2014.06.001. [PubMed: 25199954]
- 28•. Lam J, Lanphear BP, Bellinger D, Axelrad DA, McPartland J, Sutton P, et al. Developmental PBDE exposure and IQ/ADHD in childhood: a systematic review and meta-analysis. *Environ Health Perspect* 2017; 10.1289/EHP1632. A comprehensive and systematic review of the PBDE literature confirming a strong relationship between early life exposure and adverse cognitive and behavioral outcomes in children.
29. Tilson HA, MacPhail RC, Crofton KM. Defining neurotoxicity in a decision-making context. *Neurotoxicology*. 1995;16(2):363–75. [PubMed: 7566695]
30. Patisaul HB, Belcher SM. Endocrine disruptors, brain, and behaviors Oxford series in behavioral neuroendocrinology. New York: Oxford University Press; 2017.
31. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev* 2009;30(4): 293–342. 10.1210/er.2009-0002. [PubMed: 19502515]
- 32•. Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, et al. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. *Endocrinology*. 2012;153(9):4097–110. 10.1210/en.2012-1422. [PubMed: 22733974] A high-impact, thorough assessment of EDC-related effects on human health including impacts on neurodevelopment and behavior.
33. Schug TT, Blawas AM, Gray K, Heindel JJ, Lawler CP. Elucidating the links between endocrine disruptors and neurodevelopment. *Endocrinology*. 2015;156(6):1941–51. 10.1210/en.2014-1734. [PubMed: 25714811]
34. Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environ Health Perspect* 2005;113(7):894–9. 10.1289/ehp.7688. [PubMed: 16002379]
35. Landrigan PJ, Whitworth RH, Baloh RW, Staehling NW, Barthel WF, Rosenblum BF. Neuropsychological dysfunction in children with chronic low-level lead absorption. *Lancet*. 1975;1(7909): 708–12. [PubMed: 47481]

36. Needleman HL, Gunnoe C, Leviton A, Reed R, Peresie H, Maher C, et al. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. *N Engl J Med* 1979; 300(13): 689–95. 10.1056/NEJM197903293001301. [PubMed: 763299]
37. Baranowska-Bosiacka I, Gutowska I, Marchlewicz M, Marchetti C, Kurzawski M, Dziedzicko V, et al. Disrupted pro- and antioxidative balance as a mechanism of neurotoxicity induced by perinatal exposure to lead. *Brain Res* 2012;1435:56–71. 10.1016/j.brainres.2011.11.062. [PubMed: 22197700]
38. Devi CB, Reddy GH, Prasanthi RP, Chetty CS, Reddy GR. Developmental lead exposure alters mitochondrial monoamine oxidase and synaptosomal catecholamine levels in rat brain. *Int J Dev Neurosci* 2005;23(4):375–81. 10.1016/j.ijdevneu.2004.11.003. [PubMed: 15927761]
39. McGivern RF, Sokol RZ, Berman NG. Prenatal lead exposure in the rat during the third week of gestation: long-term behavioral, physiological, and anatomical effects associated with reproduction. *Toxicol Appl Pharmacol* 1991;110(2):206–15. 10.1016/S0041-008X(05)80003-1. [PubMed: 1909817]
40. Sobin C, Montoya MG, Parisi N, Schaub T, M Cervantes, Armijos RX. Microglial disruption in young mice with early chronic lead exposure. *Toxicol Lett* 2013;220(1):44–52. 10.1016/j.toxlet.2013.04.003. [PubMed: 23598043]
41. Slotkin TA, Oliver CA, Seidler FJ. Critical periods for the role of oxidative stress in the developmental neurotoxicity of chlorpyrifos and terbutaline, alone or in combination. *Brain Res Dev Brain Res* 2005;157(2):172–80. 10.1016/j.devbrainres.2005.04.001. [PubMed: 15963356]
42. Aldridge JE, Seidler FJ, Meyer A, Thillai I, Slotkin TA. Serotonergic systems targeted by developmental exposure to chlorpyrifos: effects during different critical periods. *Environ Health Perspect* 2003;111(14):1736–43. 10.1289/ehp.6489. [PubMed: 14594624]
43. Slotkin TA, Cooper EM, Stapleton HM, Seidler FJ. Does thyroid disruption contribute to the developmental neurotoxicity of chlorpyrifos? *Environ Toxicol Pharmacol* 2013;36(2):284–7. 10.1016/j.etap.2013.04.003. [PubMed: 23686008]
44. Gomez-Gimenez B, Llansola M, Hernandez-Rabaza V, Cabrera-Pastor A, Malaguarnera M, Agusti A, et al. Sex-dependent effects of developmental exposure to different pesticides on spatial learning. The role of induced neuroinflammation in the hippocampus. *Food Chem Toxicol* 2017;99:135–48. 10.1016/j.fct.2016.11.028. [PubMed: 27908700]
45. Kabuto H, Amakawa M, Shishibori T. Exposure to bisphenol A during embryonic/fetal life and infancy increases oxidative injury and causes underdevelopment of the brain and testis in mice. *Life Sci* 2004;74(24):2931–40. 10.1016/j.lfs.2003.07.060. [PubMed: 15051418]
46. Franssen D, Gerard A, Hennuy B, Donneau AF, Bourguignon JP, Parent AS. Delayed neuroendocrine sexual maturation in female rats after a very low dose of bisphenol A through altered GABAergic neurotransmission and opposing effects of a high dose. *Endocrinology*. 2016;157(5):1740–50. 10.1210/en.2015-1937. [PubMed: 26950200]
47. Patisaul HB, Sullivan AW, Radford ME, Walker DM, Adewale HB, Winnik B, et al. Anxiogenic effects of developmental bisphenol A exposure are associated with gene expression changes in the juvenile rat amygdala and mitigated by soy. *PLoS One*. 2012;7(9):e43890 10.1371/journal.pone.0043890. [PubMed: 22957036]
48. Rebuli ME, Gibson P, Rhodes CL, Cushing BS, Patisaul HB. Sex differences in microglial colonization and vulnerabilities to endocrine disruption in the social brain. *Gen Comp Endocrinol* 2016;238:39–46. 10.1016/j.ygcen.2016.04.018. [PubMed: 27102938] Important study showing sex-specific alterations in microglia colonization of the hippocampus and amygdala in rats following developmental exposure to BPA.
49. He P, He W, Wang A, Xia T, Xu B, Zhang M, et al. PBDE-47-induced oxidative stress, DNA damage and apoptosis in primary cultured rat hippocampal neurons. *Neurotoxicology*. 2008;29(1): 124–9. 10.1016/j.neuro.2007.10.002. [PubMed: 18054389]
50. Viberg H, Fredriksson A, Eriksson P. Neonatal exposure to polybrominated diphenyl ether (PBDE 153) disrupts spontaneous behaviour, impairs learning and memory, and decreases hippocampal cholinergic receptors in adult mice. *Toxicol Appl Pharmacol* 2003;192(2):95–106. 10.1016/S0041-008X(03)00217-5. [PubMed: 14550744]

51. Kodavanti PR, Coburn CG, Moser VC, MacPhail RC, Fenton SE, Stoker TE, et al. Developmental exposure to a commercial PBDE mixture, DE-71: neurobehavioral, hormonal, and reproductive effects. *Toxicol Sci* 2010;116(1):297–312. 10.1093/toxsci/kfq105. [PubMed: 20375078]
52. Mariani A, Fanelli R, Re Depaolini A, De Paola M. Decabrominated diphenyl ether and methylmercury impair fetal nervous system development in mice at documented human exposure levels. *Dev Neurobiol* 2015;75(1):23–38. 10.1002/dneu.22208. [PubMed: 25044829]
53. Moller M, Swanepoel T, Harvey BH. Neurodevelopmental animal models reveal the convergent role of neurotransmitter systems, inflammation, and oxidative stress as biomarkers of schizophrenia: implications for novel drug development. *ACS Chem Neurosci* 2015;6(7):987–1016. 10.1021/cn5003368. [PubMed: 25794269]
54. Wells PG, Bhatia S, Drake DM, Miller-Pinsler L. Fetal oxidative stress mechanisms of neurodevelopmental deficits and exacerbation by ethanol and methamphetamine. *Birth Defects Res C Embryo Today*. 2016;108(2):108–30. 10.1002/bdrc.21134. [PubMed: 27345013]
55. Ikonomidou C, Kaindl AM. Neuronal death and oxidative stress in the developing brain. *Antioxid Redox Signal*. 2011;14(8):1535–50. 10.1089/ars.2010.3581. [PubMed: 20919934]
56. Shoji H, Ikeda N, Hosozawa M, Ohkawa N, Matsunaga N, Suganuma H, et al. Oxidative stress early in infancy and neurodevelopmental outcome in very low-birthweight infants. *Pediatr Int* 2014;56(5):709–13. 10.1111/ped.12332. [PubMed: 24617865]
57. O'Donovan DJ, Fernandes CJ. Free radicals and diseases in premature infants. *Antioxid Redox Signal*. 2004;6(1):169–76. 10.1089/152308604771978471. [PubMed: 14713348]
58. Shelton JF, Hertz-Picciotto I, Pessah IN. Tipping the balance of autism risk: potential mechanisms linking pesticides and autism. *Environ Health Perspect* 2012;120(7):944–51. 10.1289/ehp.1104553. [PubMed: 22534084]
59. Kaur P, Radotra B, Minz RW, Gill KD. Impaired mitochondrial energy metabolism and neuronal apoptotic cell death after chronic dichlorvos (OP) exposure in rat brain. *Neurotoxicology*. 2007;28(6):1208–19. 10.1016/j.neuro.2007.08.001. [PubMed: 17850875]
60. Shi X, Gu A, Ji G, Li Y, Di J, Jin J, et al. Developmental toxicity of cypermethrin in embryo-larval stages of zebrafish. *Chemosphere*. 2011;85(6):1010–6. 10.1016/j.chemosphere.2011.07.024. [PubMed: 21840035]
61. Prakash C, Soni M, Kumar V. Biochemical and molecular alterations following arsenic-induced oxidative stress and mitochondrial dysfunction in rat brain. *Biol Trace Elem Res* 2015;167(1):121–9. 10.1007/s12011-015-0284-9. [PubMed: 25764338]
62. Bjorling-Poulsen M, Andersen HR, Grandjean P. Potential developmental neurotoxicity of pesticides used in Europe. *Environ Health*. 2008;7(1):50. 10.1186/1476-069X-7-50. [PubMed: 18945337]
63. Aldridge JE, Levin ED, Seidler FJ, Slotkin TA. Developmental exposure of rats to chlorpyrifos leads to behavioral alterations in adulthood, involving serotonergic mechanisms and resembling animal models of depression. *Environ Health Perspect* 2005;113(5):527–31. 10.1289/ehp.7867. [PubMed: 15866758]
64. Aldridge JE, Seidler FJ, Slotkin TA. Developmental exposure to chlorpyrifos elicits sex-selective alterations of serotonergic synaptic function in adulthood: critical periods and regional selectivity for effects on the serotonin transporter, receptor subtypes, and cell signaling. *Environ Health Perspect* 2004;112(2):148–55. [PubMed: 14754568]
65. Slotkin TA, Seidler FJ. The alterations in CNS serotonergic mechanisms caused by neonatal chlorpyrifos exposure are permanent. *Brain Res Dev Brain Res* 2005;158(1–2):115–9. 10.1016/j.devbrainres.2005.06.008. [PubMed: 16024092]
66. Slotkin TA, Seidler FJ. Comparative developmental neurotoxicity of organophosphates in vivo: transcriptional responses of pathways for brain cell development, cell signaling, cytotoxicity and neurotransmitter systems. *Brain Res Bull*. 2007;72(4–6):232–74. 10.1016/j.brainresbull.2007.01.005. [PubMed: 17452286]
67. Johri A, Yadav S, Singh RL, Dhawan A, Ali M, Parmar D. Long lasting effects of prenatal exposure to deltamethrin on cerebral and hepatic cytochrome P450s and behavioral activity in rat offspring. *Eur J Pharmacol* 2006;544(1–3):58–68. 10.1016/j.ejphar.2006.06.042. [PubMed: 16859670]

68. Shafer TJ, Meyer DA, Crofton KM. Developmental neurotoxicity of pyrethroid insecticides: critical review and future research needs. *Environ Health Perspect* 2005;113(2):123–36. [PubMed: 15687048]
69. Richardson JR, Taylor MM, Shalat SL, Guillot TS, 3rd, Caudle WM, Hossain MM, et al. Developmental pesticide exposure reproduces features of attention deficit hyperactivity disorder. *FASEB J* 2015;29(5):1960–72. 10.1096/fj.14-260901. [PubMed: 25630971]
70. Mubarak Hossain M, Suzuki T, Sato N, Sato I, Takewaki T, Suzuki K, et al. Differential effects of pyrethroid insecticides on extracellular dopamine in the striatum of freely moving rats. *Toxicol Appl Pharmacol* 2006;217(1):25–34. 10.1016/j.taap.2006.07.011. [PubMed: 16956637]
71. Elwan MA, Richardson JR, Guillot TS, Caudle WM, Miller GW. Pyrethroid pesticide-induced alterations in dopamine transporter function. *Toxicol Appl Pharmacol* 2006;211(3):188–97. 10.1016/j.taap.2005.06.003. [PubMed: 16005927]
72. Gillette JS, Bloomquist JR. Differential up-regulation of striatal dopamine transporter and alpha-synuclein by the pyrethroid insecticide permethrin. *Toxicol Appl Pharmacol* 2003;192(3):287–93. 10.1016/S0041-008X(03)00326-0. [PubMed: 14575646]
73. Kung TS, Richardson JR, Cooper KR, White LA. Developmental deltamethrin exposure causes persistent changes in dopaminergic gene expression, neurochemistry, and locomotor activity in zebrafish. *Toxicol Sci* 2015;146(2):235–43. 10.1093/toxsci/kfv087. [PubMed: 25912032]
74. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and Parkinson's disease: an umbrella review of meta-analyses. *Parkinsonism Relat Disord*. 2016;23:1–9. 10.1016/j.parkreldis.2015.12.008. [PubMed: 26739246]
75. Landrigan PJ, Benbrook C. GMOs, herbicides, and public health. *N Engl J Med* 2015;373(8):693–5. 10.1056/NEJMp1505660. [PubMed: 26287848]
76. Puzianowska-Kuznicka M, Pietrzak M, Turowska O, Nauman A. Thyroid hormones and their receptors in the regulation of cell proliferation. *Acta Biochim Pol* 2006;53(4):641–50. [PubMed: 17115080]
77. Ahmed OM, El-Gareib AW, El-Bakry AM, Abd El-Tawab SM, Ahmed RG. Thyroid hormones states and brain development interactions. *Int J Dev Neurosci* 2008;26(2):147–209. 10.1016/j.ijdevneu.2007.09.011. [PubMed: 18031969]
78. Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. *Endocr Rev* 2010;31(2):139–70. 10.1210/er.2009-0007. [PubMed: 20051527]
79. Pinson A, Bourguignon JP, Parent AS. Exposure to endocrine disrupting chemicals and neurodevelopmental alterations. *Andrology*. 2016;4(4):706–22. 10.1111/andr.12211. [PubMed: 27285165]
80. Zoeller RT, Crofton KM. Thyroid hormone action in fetal brain development and potential for disruption by environmental chemicals. *Neurotoxicology*. 2000;21(6):935–45. [PubMed: 11233763]
81. Frye CA, Bo E, Calamandrei G, Calza L, Dessi-Fulgheri F, Fernandez M, et al. Endocrine disruptors: a review of some sources, effects, and mechanisms of actions on behaviour and neuroendocrine systems. *J Neuroendocrinol* 2012;24(1):144–59. 10.1111/j.1365-2826.2011.02229.x. [PubMed: 21951193]
82. Rebuli ME, Patisaul HB. Assessment of sex specific endocrine disrupting effects in the prenatal and pre-pubertal rodent brain. *J Steroid Biochem Mol Biol* 2015; 10.1016/j.jsbmb.2015.08.021. Important summary of the molecular and neuroanatomical changes in the pre-adult rodent brain following developmental exposure to EDCs, with a focus on sex differences.
83. Wolstenholme JT, Rissman EF, Connelly JJ. The role of bisphenol A in shaping the brain, epigenome and behavior. *Horm Behav* 2011;59(3):296–305. 10.1016/j.yhbeh.2010.10.001. [PubMed: 21029734]
84. Dickerson SM, Gore AC. Estrogenic environmental endocrine-disrupting chemical effects on reproductive neuroendocrine function and dysfunction across the life cycle. *Rev Endocr Metab Disord* 2007;8(2):143–59. 10.1007/s11154-007-9048-y. [PubMed: 17674209]
85. Patisaul HB, Adewale HB. Long-term effects of environmental endocrine disruptors on reproductive physiology and behavior. *Front Behav Neurosci* 2009;3:10 10.3389/neuro.08.010.2009. [PubMed: 19587848]

86. Cao J, Joyner L, Mickens JA, Leyrer SM, Patisaul HB. Sex-specific *Esr2* mRNA expression in the rat hypothalamus and amygdala is altered by neonatal bisphenol A exposure. *Reproduction*. 2014;147(4):537–54. 10.1530/REP-13-0501. [PubMed: 24352099]
87. Rubin BS, Lenkowski JR, Schaeberle CM, Vandenberg LN, Ronsheim PM, Soto AM. Evidence of altered brain sexual differentiation in mice exposed perinatally to low, environmentally relevant levels of bisphenol A. *Endocrinology*. 2006;147(8):3681–91. 10.1210/en.2006-0189. [PubMed: 16675520]
88. Foradori CD, Hinds LR, Hanneman WH, Handa RJ. Effects of atrazine and its withdrawal on gonadotropin-releasing hormone neuroendocrine function in the adult female Wistar rat. *Biol Reprod* 2009;81(6):1099–105. 10.1095/biolreprod.109.077453. [PubMed: 19605789]
89. Foradori CD, Hinds LR, Hanneman WH, Legare ME, Clay CM, Handa RJ. Atrazine inhibits pulsatile luteinizing hormone release without altering pituitary sensitivity to a gonadotropin-releasing hormone receptor agonist in female Wistar rats. *Biol Reprod* 2009;81(1):40–5. 10.1095/biolreprod.108.075713. [PubMed: 19299313]
90. Foradori CD, Zimmerman AD, Hinds LR, Zuloaga KL, Breckenridge CB, Handa RJ. Atrazine inhibits pulsatile gonadotropin-releasing hormone (GnRH) release without altering GnRH messenger RNA or protein levels in the female rat. *Biol Reprod* 2013;88(1):9. 10.1095/biolreprod.112.102277. [PubMed: 23197165]
91. Sullivan AW, Beach EC, Stetzk LA, Perry A, D'Addezio AS, Cushing BS, et al. A novel model for neuroendocrine toxicology: neurobehavioral effects of BPA exposure in a prosocial species, the prairie vole (*Microtus ochrogaster*). *Endocrinology*. 2014;155(10):3867–81. 10.1210/en.2014-1379. [PubMed: 25051448]
92. Engell MD, Godwin J, Young LJ, Vandenberg JG. Perinatal exposure to endocrine disrupting compounds alters behavior and brain in the female pine vole. *Neurotoxicol Teratol* 2006;28(1):103–10. 10.1016/j.ntt.2005.10.002. [PubMed: 16307867]
93. Tabb MM, Blumberg B. New modes of action for endocrine-disrupting chemicals. *Mol Endocrinol*. 2006;20(3):475–82. 10.1210/me.2004-0513. [PubMed: 16037129]
94. Morse DC, Wehler EK, Wesseling W, Koeman JH, Brouwer A. Alterations in rat brain thyroid hormone status following pre- and postnatal exposure to polychlorinated biphenyls (Aroclor 1254). *Toxicol Appl Pharmacol* 1996;136(2):269–79. 10.1006/taap.1996.0034. [PubMed: 8619235]
95. Goldey ES, Kehn LS, Lau C, Rehnberg GL, Crofton KM. Developmental exposure to polychlorinated biphenyls (Aroclor 1254) reduces circulating thyroid hormone concentrations and causes hearing deficits in rats. *Toxicol Appl Pharmacol* 1995;135(1):77–88. 10.1006/taap.1995.1210. [PubMed: 7482542]
96. Gauger KJ, Kato Y, Haraguchi K, Lehmler HJ, Robertson LW, Bansal R, et al. Polychlorinated biphenyls (PCBs) exert thyroid hormone-like effects in the fetal rat brain but do not bind to thyroid hormone receptors. *Environ Health Perspect* 2004;112(5):516–23. [PubMed: 15064154]
97. Navarro VM, Sanchez-Garrido MA, Castellano JM, Roa J, Garcia-Galiano D, Pineda R, et al. Persistent impairment of hypothalamic KiSS-1 system after exposures to estrogenic compounds at critical periods of brain sex differentiation. *Endocrinology*. 2009;150(5):2359–67. 10.1210/en.2008-0580. [PubMed: 19106226]
98. Zoeller RT. Environmental chemicals impacting the thyroid: targets and consequences. *Thyroid*. 2007;17(9):811–7. 10.1089/thy.2007.0107. [PubMed: 17956155]
99. Giera S, Bansal R, Ortiz-Toro TM, Taub DG, Zoeller RT. Individual polychlorinated biphenyl (PCB) congeners produce tissue- and gene-specific effects on thyroid hormone signaling during development. *Endocrinology*. 2011;152(7):2909–19. 10.1210/en.2010-1490. [PubMed: 21540284]
100. Naveau E, Pinson A, Gerard A, Nguyen L, Charlier C, Thome JP, et al. Alteration of rat fetal cerebral cortex development after prenatal exposure to polychlorinated biphenyls. *PLoS One*. 2014;9(3):e91903. 10.1371/journal.pone.0091903. [PubMed: 24642964]
101. Cao J, Mickens JA, McCaffrey KA, Leyrer SM, Patisaul HB. Neonatal bisphenol A exposure alters sexually dimorphic gene expression in the postnatal rat hypothalamus. *Neurotoxicology*. 2012;33(1):23–36. 10.1016/j.neuro.2011.11.002. [PubMed: 22101008]

102. Cao J, Rebuli ME, Rogers J, Todd KL, Leyrer SM, Ferguson SA, et al. Prenatal bisphenol A exposure alters sex-specific estrogen receptor expression in the neonatal rat hypothalamus and amygdala. *Toxicol Sci* 2013;133(1):157–73. 10.1093/toxsci/kft035. [PubMed: 23457122]
103. Ceccarelli I, Della Seta D, Fiorenzani P, Farabollini F, Aloisi AM. Estrogenic chemicals at puberty change ERalpha in the hypothalamus of male and female rats. *Neurotoxicol Teratol* 2007;29(1): 108–15. 10.1016/j.ntt.2006.10.011. [PubMed: 17157476]
104. Colciago A, Casati L, Mornati O, Vergoni AV, Santagostino A, Celotti F, et al. Chronic treatment with polychlorinated biphenyls (PCB) during pregnancy and lactation in the rat part 2: effects on reproductive parameters, on sex behavior, on memory retention and on hypothalamic expression of aromatase and 5alpha-reductases in the offspring. *Toxicol Appl Pharmacol* 2009;239(1):46–54. 10.1016/j.taap.2009.04.023. [PubMed: 19464308]
105. Lichtensteiger W, Bassetti-Gaille C, Faass O, Axelstad M, Boberg J, Christiansen S, et al. Differential gene expression patterns in developing sexually dimorphic rat brain regions exposed to antiandrogenic, estrogenic, or complex endocrine disruptor mixtures: glutamatergic synapses as target. *Endocrinology*. 2015;156(4):1477–93. 10.1210/en.2014-1504. [PubMed: 25607892]
106. He Z, Paule MG, Ferguson SA. Low oral doses of bisphenol A increase volume of the sexually dimorphic nucleus of the preoptic area in male, but not female, rats at postnatal day 21. *Neurotoxicol Teratol* 2012;34(3):331–7. 10.1016/j.ntt.2012.03.004. [PubMed: 22507915]
107. Patisaul HB, Fortino AE, Polston EK. Differential disruption of nuclear volume and neuronal phenotype in the preoptic area by neonatal exposure to genistein and bisphenol-A. *Neurotoxicology*. 2007;28(1):1–12. 10.1016/j.neuro.2006.10.001. [PubMed: 17109964]
108. Bourguignon JP, Franssen D, Gerard A, Janssen S, Pinson A, Naveau E, et al. Early neuroendocrine disruption in hypothalamus and hippocampus: developmental effects including female sexual maturation and implications for endocrine disrupting chemical screening. *J Neuroendocrinol* 2013;25(11):1079–87. 10.1111/jne.12107. [PubMed: 24028442]
109. Xu X, Xie L, Hong X, Ruan Q, Lu H, Zhang Q, et al. Perinatal exposure to bisphenol-A inhibits synaptogenesis and affects the synaptic morphological development in offspring male mice. *Chemosphere*. 2013;91(8):1073–81. 10.1016/j.chemosphere.2012.12.065. [PubMed: 23490186]
110. Eiland L, Ramroop J, Hill MN, Manley J, McEwen BS. Chronic juvenile stress produces corticolimbic dendritic architectural re-modeling and modulates emotional behavior in male and female rats. *Psychoneuroendocrinology*. 2012;37(1):39–47. 10.1016/j.psyneuen.2011.04.015. [PubMed: 21658845]
111. Carrion VG, Wong SS. Can traumatic stress alter the brain? Understanding the implications of early trauma on brain development and learning. *J Adolesc Health*. 2012;51(2 Suppl):S23–8. 10.1016/j.jadohealth.2012.04.010. [PubMed: 22794529]
112. McCormick CM, Mathews IZ. Adolescent development, hypothalamic-pituitary-adrenal function, and programming of adult learning and memory. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(5):756–65. 10.1016/j.pnpbp.2009.09.019.
113. Glover V, O'Connor TG, O'Donnell K. Prenatal stress and the programming of the HPA axis. *Neurosci Biobehav Rev* 2010;35(1):17–22. 10.1016/j.neubiorev.2009.11.008. [PubMed: 19914282]
114. O'Donnell K, O'Connor TG, Glover V. Prenatal stress and neurodevelopment of the child: focus on the HPA axis and role of the placenta. *Dev Neurosci* 2009;31(4):285–92. 10.1159/000216539. [PubMed: 19546565]
115. Romeo RD. The impact of stress on the structure of the adolescent brain: implications for adolescent mental health. *Brain Res* 2017;1654(Pt B):185–91. 10.1016/j.brainres.2016.03.021. [PubMed: 27021951]
116. Bale TL. Sex differences in prenatal epigenetic programming of stress pathways. *Stress*. 2011;14(4):348–56. 10.3109/10253890.2011.586447. [PubMed: 21663536] Excellent review of the role epigenetics plays in shaping the developing brain including sexual dimorphisms.
117. Gillette R, Reilly MP, Topper VY, Thompson LM, Crews D, Gore AC. Anxiety-like behaviors in adulthood are altered in male but not female rats exposed to low dosages of polychlorinated biphenyls in utero. *Horm Behav* 2017;87:8–15. 10.1016/j.yhbeh.2016.10.011. [PubMed: 27794483]

118. Reilly MP, Weeks CD, Topper VY, Thompson LM, Crews D, Gore AC. The effects of prenatal PCBs on adult social behavior in rats. *Horm Behav* 2015;73:47–55. 10.1016/j.yhbeh.2015.06.002. [PubMed: 26093262]
119. Meserve LA, Murray BA, Landis JA. Influence of maternal ingestion of Aroclor 1254 (PCB) or FireMaster BP-6 (PBB) on unstimulated and stimulated corticosterone levels in young rats. *Bull Environ Contam Toxicology*. 1992;48(5):715–20.
120. Chen F, Zhou L, Bai Y, Zhou R, Chen L. Sex differences in the adult HPA axis and affective behaviors are altered by perinatal exposure to a low dose of bisphenol A. *Brain Res* 2014;1571:12–24. 10.1016/j.brainres.2014.05.010. [PubMed: 24857958]
121. Ransohoff RM, Brown MA. Innate immunity in the central nervous system. *J Clin Invest* 2012;122(4):1164–71. 10.1172/JCI58644. [PubMed: 22466658]
122. Madhusudan A, Vogel P, Knuesel I. Impact of prenatal immune system disturbances on brain development. *J NeuroImmune Pharmacol* 2013;8(1):79–86. 10.1007/s11481-012-9374-z. [PubMed: 22580757]
123. Muller N, Myint AM, Schwarz MJ. The impact of neuroimmune dysregulation on neuroprotection and neurotoxicity in psychiatric disorders—relation to drug treatment. *Dialogues Clin Neurosci* 2009;11(3):319–32. [PubMed: 19877499]
124. Bilbo SD, Schwarz JM. Early-life programming of later-life brain and behavior: a critical role for the immune system. *Front Behav Neurosci* 2009;3:14. 10.3389/neuro.08.014.2009. [PubMed: 19738918]
125. Bilbo SD, Schwarz JM. The immune system and developmental programming of brain and behavior. *Front Neuroendocrinol* 2012;33(3):267–86. 10.1016/j.yfrne.2012.08.006. [PubMed: 22982535]
126. Ullian EM, Christopherson KS, Barres BA. Role for glia in synaptogenesis. *Glia*. 2004;47(3):209–16. 10.1002/glia.20082. [PubMed: 15252809]
127. Rakic S, Zecevic N. Programmed cell death in the developing human telencephalon. *Eur J Neurosci* 2000;12(8):2721–34. 10.1046/j.1460-9568.2000.00153.x. [PubMed: 10971615]
128. Streit WJ. Microglia and macrophages in the developing CNS. *Neurotoxicology*. 2001;22(5):619–24. 10.1016/S0161-813X(01)00033-X. [PubMed: 11770883]
129. Nawa H, Takei N. Recent progress in animal modeling of immune inflammatory processes in schizophrenia: implication of specific cytokines. *Neurosci Res* 2006;56(1):2–13. 10.1016/j.neures.2006.06.002. [PubMed: 16837094]
130. Ransohoff RM, Schafer D, Vincent A, Blachere NE, Bar-Or A. Neuroinflammation: ways in which the immune system affects the brain. *Neurotherapeutics*. 2015;12(4):896–909. 10.1007/s13311-015-0385-3. [PubMed: 26306439]
131. Shi L, Fatemi SH, Sidwell RW, Patterson PH. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *J Neurosci* 2003;23(1):297–302. [PubMed: 12514227]
132. Cai Z, Pan ZL, Pang Y, Evans OB, Rhodes PG. Cytokine induction in fetal rat brains and brain injury in neonatal rats after maternal lipopolysaccharide administration. *Pediatr Res* 2000;47(1):64–72. 10.1203/00006450-200001000-00013. [PubMed: 10625084]
133. Meyer U, Feldon J, Schedlowski M, Yee BK. Immunological stress at the maternal-foetal interface: a link between neurodevelopment and adult psychopathology. *Brain Behav Immun* 2006;20(4):378–88. 10.1016/j.bbi.2005.11.003. [PubMed: 16378711]
134. Pang Y, Cai Z, Rhodes PG. Disturbance of oligodendrocyte development, hypomyelination and white matter injury in the neonatal rat brain after intracerebral injection of lipopolysaccharide. *Brain Res Dev Brain Res* 2003;140(2):205–14. 10.1016/S0165-3806(02)00606-5. [PubMed: 12586426]
135. Deverman BE, Patterson PH. Cytokines and CNS development. *Neuron*. 2009;64(1):61–78. 10.1016/j.neuron.2009.09.002. [PubMed: 19840550]
136. Tremblay ME, Stevens B, Sierra A, Wake H, Bessis A, Nimmerjahn A. The role of microglia in the healthy brain. *J Neurosci* 2011;31(45):16064–9. 10.1523/JNEUROSCI.4158-11.2011. [PubMed: 22072657]

137. Bruce-Keller AJ, Keeling JL, Keller JN, Huang FF, Camondola S, Mattson MP. Antiinflammatory effects of estrogen on microglial activation. *Endocrinology*. 2000;141(10):3646–56. 10.1210/endo.141.10.7693. [PubMed: 11014219]
138. Vegeto E, Bonincontro C, Pollio G, Sala A, Viappiani S, Nardi F, et al. Estrogen prevents the lipopolysaccharide-induced inflammatory response in microglia. *J Neurosci* 2001;21(6):1809–18. [PubMed: 11245665]
139. Ishihara Y, Itoh K, Ishida A, Yamazaki T. Selective estrogen-receptor modulators suppress microglial activation and neuronal cell death via an estrogen receptor-dependent pathway. *J Steroid Biochem Mol Biol* 2015;145:85–93. 10.1016/j.jsbmb.2014.10.002. [PubMed: 25305410]
140. Wise LM, Sadowski RN, Kim T, Willing J, Juraska JM. Long-term effects of adolescent exposure to bisphenol A on neuron and glia number in the rat prefrontal cortex: differences between the sexes and cell type. *Neurotoxicology*. 2016;53:186–92. 10.1016/j.neuro.2016.01.011. [PubMed: 26828634] Critical study showing long-term changes in the number of glial cells in the prefrontal cortex of rats following adolescent exposure to BPA.
141. Parkhurst CN, Yang G, Ninan I, Savas JN, Yates JR, 3rd, Lafaille JJ, et al. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. *Cell*. 2013;155(7): 1596–609. 10.1016/j.cell.2013.11.030. [PubMed: 24360280]
142. Faleiros BE, Miranda AS, Campos AC, Gomides LF, Kangussu LM, Guatimosim C, et al. Up-regulation of brain cytokines and chemokines mediates neurotoxicity in early acute liver failure by a mechanism independent of microglial activation. *Brain Res* 2014;1578:49–59. 10.1016/j.brainres.2014.07.001. [PubMed: 25017944]
143. Garay PA, Hsiao EY, Patterson PH, McAllister AK. Maternal immune activation causes age- and region-specific changes in brain cytokines in offspring throughout development. *Brain Behav Immun* 2013;31:54–68. 10.1016/j.bbi.2012.07.008. [PubMed: 22841693]
144. Azcoitia I, Sierra A, Garcia-Segura LM. Localization of estrogen receptor beta-immunoreactivity in astrocytes of the adult rat brain. *Glia*. 1999;26(3):260–7. 10.1002/(SICI)1098-1136(199905)26:3<260::AID-GLIA7>3.0.CO;2-R. [PubMed: 10340766]
145. Arvanitis DN, Wang H, Bagshaw RD, Callahan JW, Boggs JM. Membrane-associated estrogen receptor and caveolin-1 are present in central nervous system myelin and oligodendrocyte plasma membranes. *J Neurosci Res* 2004;75(5):603–13. 10.1002/jnr.20017. [PubMed: 14991836]
146. Jones KA, Thomsen C. The role of the innate immune system in psychiatric disorders. *Mol Cell Neurosci* 2013;53:52–62. 10.1016/j.mcn.2012.10.002. [PubMed: 23064447]
147. Fatemi SH, Reutiman TJ, Folsom TD, Huang H, Oishi K, Mori S, et al. Maternal infection leads to abnormal gene regulation and brain atrophy in mouse offspring: implications for genesis of neurodevelopmental disorders. *Schizophr Res* 2008;99(1–3):56–70. 10.1016/j.schres.2007.11.018. [PubMed: 18248790]
148. Mokarizadeh A, Faryabi MR, Rezvanfar MA, Abdollahi M. A comprehensive review of pesticides and the immune dysregulation: mechanisms, evidence and consequences. *Toxicol Mech Methods*. 2015;25(4):258–78. 10.3109/15376516.2015.1020182. [PubMed: 25757504]
149. Rogers JA, Metz L, Yong VW. Review: endocrine disrupting chemicals and immune responses: a focus on bisphenol-A and its potential mechanisms. *Mol Immunol* 2013;53(4):421–30. 10.1016/j.molimm.2012.09.013. [PubMed: 23123408]
150. Xu H, Yang M, Qiu W, Pan C, Wu M. The impact of endocrinedisrupting chemicals on oxidative stress and innate immune response in zebrafish embryos. *Environ Toxicol Chem* 2013;32(8): 1793–9. 10.1002/etc.2245. [PubMed: 23606268]
151. Liao SL, Tsai MH, Lai SH, Yao TC, Hua MC, Yeh KW, et al. Prenatal exposure to bisphenol-A is associated with Toll-like receptor-induced cytokine suppression in neonates. *Pediatr Res* 2016;79(3):438–44. 10.1038/pr.2015.234. [PubMed: 26571221]
152. Diamond B, Huerta PT, Tracey K, Volpe BT. It takes guts to grow a brain: increasing evidence of the important role of the intestinal microflora in neuro- and immune-modulatory functions during development and adulthood. *BioEssays*. 2011;33(8):588–91. 10.1002/bies.201100042. [PubMed: 21681774]

153. Diaz Heijtz R, Wang S, Anuar F, Qian Y, Bjorkholm B, Samuelsson A, et al. Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci U S A*. 2011;108(7):3047–52. 10.1073/pnas.1010529108. [PubMed: 21282636]
154. Myatt L Placental adaptive responses and fetal programming. *J Physiol* 2006;572(Pt 1):25–30. 10.1113/jphysiol.2006.104968. [PubMed: 16469781]
155. Bronson SL, Bale TL. The placenta as a mediator of stress effects on neurodevelopmental reprogramming. *Neuropsychopharmacology*. 2016;41(1):207–18. 10.1038/npp.2015.231. [PubMed: 26250599]
156. Bronson SL, Bale TL. Prenatal stress-induced increases in placental inflammation and offspring hyperactivity are male-specific and ameliorated by maternal antiinflammatory treatment. *Endocrinology*. 2014;155(7):2635–46. 10.1210/en.2014-1040. [PubMed: 24797632]
157. Leazer TM, Klaassen CD. The presence of xenobiotic transporters in rat placenta. *Drug Metab Dispos* 2003;31(2):153–67. 10.1124/dmd.31.2.153. [PubMed: 12527696]
158. D'Aloisio AA, DeRoo LA, Baird DD, Weinberg CR, Sandler DP. Prenatal and infant exposures and age at menarche. *Epidemiology*. 2013;24(2):277–84. 10.1097/EDE.0b013e31828062b7. [PubMed: 23348069]
159. Esteban-Vasallo MD, Aragonés N, Pollán M, López-Abente G, Pérez-Gómez B. Mercury, cadmium, and lead levels in human placenta: a systematic review. *Environ Health Perspect*. 2012;120(10):1369–77. 10.1289/ehp.1204952. [PubMed: 22591711]
160. Vizcaino E, Grimalt JO, Fernandez-Somoano A, Tardon A. Transport of persistent organic pollutants across the human placenta. *Environ Int* 2014;65:107–15. 10.1016/j.envint.2014.01.004. [PubMed: 24486968]
161. Leonetti C, Butt CM, Hoffman K, Hammel SC, Miranda ML, Stapleton HM. Brominated flame retardants in placental tissues: associations with infant sex and thyroid hormone endpoints. *Environ Health*. 2016;15(1):113 10.1186/s12940-016-0199-8. [PubMed: 27884139]
162. Leonetti C, Butt CM, Hoffman K, Miranda ML, Stapleton HM. Concentrations of polybrominated diphenyl ethers (PBDEs) and 2,4,6-tribromophenol in human placental tissues. *Environ Int* 2016;88:23–9. 10.1016/j.envint.2015.12.002. [PubMed: 26700418]
163. Baldwin KR, Phillips AL, Horman B, Arambula SE, Rebuli ME, Stapleton HM, et al. Sex specific placental accumulation and behavioral effects of developmental Firemaster® 550 exposure in Wistar rats. *Sci Rep* 2017;7(1):7118 10.1038/s41598-017-07216-6. [PubMed: 28769031]
164. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. *Nat Rev Immunol* 2011;11(9):625–32. 10.1038/nri3042. [PubMed: 21818124]

Table 1

Representative neurotoxic chemicals and how they can impact brain development through multiple mechanisms

Chemical class	Chemical name	Exposure level	Windows of exposure	Species	Oxidative stress effects	Neurotransmitter effects	Neuroendocrine effects	Immune effects	Behavioral phenotype
Metal	<i>Lead</i>	1000 ppm	Gestation and lactation	Rat	Disruption of pro- and antioxidant balance [37]				
		2000 or 10,000 ppm	Lactation	Rat		Increased synaptosomal catecholamines [38]			
		1000 ppm	Gestation	Rat			Alterations in HPG axis [39]		
OP pesticide	<i>CYPF</i>	30 or 130 ppm	Lactation	Mouse				Reduction of microglia [40]	
		1, 2, 5, 10, 20, or 40 mg/kg	Gestation and lactation	Rat	Increased biomarkers of oxidative stress [41]				
		1 or 5 mg/kg	Gestation	Rat		Disruption of serotonergic gene expression and signal transduction [42]			
Component of Plastic	<i>BPA</i>	1 or 5 mg/kg	Gestation and lactation	Rat			Reduced brain thyroxine [43]		Altered learning behavior
		0.1, 0.3, 1 mg/kg	Gestation and lactation	Rat					
		5 or 10 µg/ml	Gestation and lactation	Mouse	Increased biomarkers of oxidative stress [45]			Induced neuroinflammation [44]	
		25 mg/kg, 25 µg/kg, 5 mg/kg	Postnatal	Rat		Increased inhibitory GABA signaling [46]			
		2.5–2700 µg/kg	Gestation and lactation	Rat			Downregulation of estrogen and melanocortin receptors [47]		Anxiogenic behavior
Flame Retardant	<i>PBDEs</i>	1 mg/L, 5 µg/kg, 50 µg/kg, or 50 mg/kg	Gestation and lactation	Rat and vole				Altered microglia colonization [48•]	
		0, 2.06, 20.6, or 41.2 µM	NA	Rat (primary hippocampal neurons, isolated from fetus)	ROS production, DNA damage, and apoptosis [49]				Loss or reversal of behavioral sex differences
		0.45, 0.9, or 9.0 mg/kg	Neonatal	Mouse		Reduced cholinergic nicotinic receptors [50]			Disrupted spontaneous, learning, and memory behaviors
		1.7, 10.2, or 30.6 mg/kg	Gestation and lactation	Rat			Hypothyroxinemia in exposed dams and their offspring [51]		Cognitive impairments
		0.0075, 0.075, 0.75, or 7.5 mg/kg	Gestation	Mouse				Activation of microglia [52]	

This table is not meant to be exhaustive but instead contains representative examples from the rodent literature of each mechanism of neurotoxicity highlighted in this review. In some studies, multiple outcomes were observed. For each chemical listed, there is an abundance of confirmatory evidence demonstrating developmental neurotoxicity in other species, including humans

NA not available