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# Gene × environment interactions in autism spectrum disorders

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## Abstract

There is credible evidence that environmental factors influence individual risk and/or severity of autism spectrum disorders (hereafter referred to as autism). While it is likely that environmental chemicals contribute to the etiology of autism via multiple

mechanisms, identifying specific environmental factors that confer risk for autism and understanding how they contribute to the etiology of autism has been challenging, in part because the influence of environmental chemicals likely varies depending on the genetic substrate of the exposed individual. Current research efforts are focused on elucidating the mechanisms by which environmental chemicals interact with autism genetic susceptibilities to adversely impact neurodevelopment. The goal is to not only generate insights regarding the pathophysiology of autism, but also inform the development of screening platforms to identify specific environmental factors and gene  $\times$  environment ( $G \times E$ ) interactions that modify autism risk. Data from such studies are needed to support development of intervention strategies for mitigating the burden of this neurodevelopmental condition on individuals, their families and society. In this review, we discuss environmental chemicals identified as putative autism risk factors and proposed mechanisms by which  $G \times E$  interactions influence autism risk and/or severity using polychlorinated biphenyls (PCBs) as an example.



## 1. Introduction

Autism spectrum disorder (ASD), hereafter referred to as autism, is a complex, multifactorial neurodevelopmental condition that is defined clinically by core deficits in social reciprocity and communication, restrictive interests and repetitive behaviors. The severity of core symptoms, the expression of co-morbidities, which include intellectual disability, anxiety, seizures, gastrointestinal disturbances, and immunological abnormalities, and the response to treatment vary considerably between individuals diagnosed with autism (Lord, Elsabbagh, Baird, & Veenstra-Vanderweele, 2018). The United States (U.S.) Center for Disease Control (CDC) estimated the prevalence of autism in U.S. children in 2021 to be 1 in 44, which is more than three times the CDC 2002 estimate of 1 in 150 U.S. children (<https://www.autism-society.org>). This trend of rising rates of autism, which dates back to the early 1990s, is a global occurrence not confined to the U.S. (Zeidan et al., 2022). Large-scale surveys estimate the current median worldwide prevalence of autism to be 1 in 100 children (Zeidan et al., 2022). When considered in the context of the tremendous costs that autism exacts on affected individuals, their families, and society (Hong et al., 2020; Leibson et al., 2020; Schofield et al., 2019), these statistics underscore the need to identify factors that confer autism risk and/or modify symptom severity.

Research on the etiology of autism has identified a strong hereditary component (Buxbaum & Hof, 2011; El-Fishawy & State, 2010; Geschwind, 2011). The candidate genes most strongly associated with autism encode

proteins that regulate the patterning of synaptic connections in the developing brain (Delorme et al., 2013; Guang et al., 2018; Landrigan, Lambertini, & Birnbaum, 2012; Masini et al., 2020; Qiu, Aldinger, & Levitt, 2012; Stamou, Streifel, Goines, & Lein, 2013). However, genetic research has also shown that genes linked to autism rarely segregate in a simple Mendelian fashion (El-Fishawy & State, 2010) and that solely genetic causes account for approximately 10–30% of all autism cases (Ansel, Rosenzweig, Zisman, Melamed, & Gesundheit, 2016; Lai, Lombardo, & Baron, 2014; Masini et al., 2020). Moreover, there is incomplete concordance of autism in monozygotic twins (Herbert, 2010), and even in genetic syndromes strongly associated with autism, a significant percentage of carriers do not express autism phenotypes (Herbert, 2010; Levitt & Campbell, 2009; Masini et al., 2020). These observations are consistent with a model in which environmental factors act as modifiers of autism risk genes.

While the dramatic increase in autism rates over the past several decades is often presented as evidence that environmental factors are involved in autism, others have argued that the progressive rise in autism is the result of diagnostic substitution, or the labeling of individuals as autistic who previously would not have been so labeled, due to broadening of diagnostic criteria, coupled with increased awareness and improved detection of these disorders (Bishop, Whitehouse, Watt, & Line, 2008; Coo et al., 2008; Parner, Schendel, & Thorsen, 2008). However, studies that have tested this hypothesis found that diagnostic substitution accounted for less than half of new cases, indicating there has been a true increase in the number of individuals diagnosed with autism (Grether, Rosen, Smith, & Croen, 2009; Hertz-Picciotto & Delwiche, 2009; Hertz-Picciotto, Schmidt, & Krakowiak, 2018; King & Bearman, 2009). Consistent with these conclusions, two well-powered independent twin studies (Frazier et al., 2014; Hallmayer et al., 2011) and a third study of more than 14,000 Swedish children with autism (Sandin et al., 2014) concluded that environmental factors account for approximately 50–60% of autism cases. Collectively, these studies suggest that environmental factors can significantly influence autism susceptibility, thereby providing a plausible explanation for both the marked increase in autism rates and the significant clinical heterogeneity of autism.

In contrast to genetic risks, which are currently irreversible, environmental factors are modifiable risk factors. The identification of specific environmental factors that increase autism risk would enable the primary prevention of autism via public health policies aimed at reducing relevant

environmental exposures in susceptible populations. Progress has been made in identifying environmental risk factors for autism, which include advanced paternal age at conception, complications during pregnancy, maternal diet, and prenatal exposure to psychotropic drugs (Bolte, Girdler, & Marschik, 2019; Carlsson, Molander, Taylor, Jonsson, & Bolte, 2020). Environmental chemical contaminants have also been proposed as autism risk factors (Landrigan, 2010; Landrigan et al., 2012). While experimental animal and predictive toxicology studies have identified environmental chemicals associated with autism-relevant phenotypes, it has been challenging to demonstrate this association in human studies (Carter & Blizard, 2016; Kalkbrenner, Schmidt, & Penlesky, 2014; Pelch, Bolden, & Kwiatkowski, 2019; Rock & Patisaul, 2018; Rossignol, Genuis, & Frye, 2014). A recent analysis of the relevant epidemiological literature concluded that overall, these studies were moderate in quality and of limited strength (Mari-Bauset et al., 2022). The authors identified numerous methodological challenges associated with epidemiological studies of environmental influences in autism that decreased quality and strength. These included difficulties in obtaining accurate measures of exposure, particularly for chemicals with short half-lives, such as some of the pesticides, phthalates and BPA; controlling for confounding factors, especially socio-economic stressors that tend to co-vary with environmental exposures; and dealing with co-exposures, a not insignificant issue given the number of chemicals in the human chemosphere that vary in both composition and concentration across time and space. Epidemiologic studies of complex neurodevelopmental conditions face additional challenges in that these conditions are phenotypically and genetically heterogeneous. The former presents diagnostic challenges, while the latter likely creates a range of sensitivities to environmental risk factors (Pessah & Lein, 2008) that masks clear associations between exposure and diagnosis.

As a result of the difficulties associated with using epidemiological approaches to identify environmental chemicals that confer risk for autism, animal and cell-based models that demonstrate effects of environmental chemicals on outcomes with face validity to autism phenotypes are critically important for corroborating and informing human studies. Since autism is diagnosed based on behavioral criteria that are not readily translated to animal models, a key challenge has been identifying autism-relevant molecular and cellular phenotypes that can be quantified in experimental models, including cell-based and predictive toxicology models. An exciting advance in this regard is the convergence of genetic, histologic, *in vivo* imaging and

functional data on altered patterns of synaptic connectivity as the biological basis underlying the behavioral phenotypes associated with autism (Alamdari, Sadeghi Damavandi, Zarei, & Khosrowabadi, 2022; Bourgeron, 2009; Geschwind & Levitt, 2007; Guang et al., 2018; Persichetti, Shao, Gotts, & Martin, 2022; Rubenstein & Merzenich, 2003; Zoghbi & Bear, 2012). As indicated earlier, candidate genes most strongly implicated in the causation of autism encode proteins that regulate the patterning of neuronal networks during development and influence the balance of excitatory to inhibitory signaling in the brain or E/I balance (Ansel et al., 2016; Bourgeron, 2009; Rubenstein & Merzenich, 2003; Stamou et al., 2013; Zoghbi & Bear, 2012). Histological analyses have identified abnormalities of dendritic and synaptic morphology (Penzes, Cahill, Jones, VanLeeuwen, & Woolfrey, 2011). For example, spine density was increased in Golgi-impregnated pyramidal neurons of Layer II in the frontal, temporal and parietal lobes and Layer V of the temporal lobe in autism (Hutsler & Zhang, 2010), suggesting skewed cortical synaptic activity towards excitation. Abnormal spine morphology was observed in the temporal and visual cortices of patients with Fragile-X, a genetic syndrome with a high incidence of autism (Irwin et al., 2001). Neuroimaging studies of children with autism have revealed both hypo- and hyper-connectivity in the brain of affected individuals (Baribeau & Anagnostou, 2013; Therien, Degre-Pelletier, Barbeau, Samson, & Soulieres, 2022). The available functional MRI data support a pattern of early brain overgrowth in the first few years of life followed by aberrant maturation in adolescence with impaired long-range connectivity but increased local and/or subcortical connectivity (reviewed in Baribeau & Anagnostou, 2013).

The differences in synaptic connectivity observed in individuals with autism may reflect influences of sex (Alaerts, Swinnen, & Wenderoth, 2016) and/or genotype (Dennis et al., 2011; Rudie et al., 2012; Scott-Van Zeeland et al., 2010). As an example of genotype, functional MRI studies of individuals expressing the autism risk variant of the Met Receptor Tyrosine Kinase (MET) gene revealed unique brain activity in response to social stimuli and altered connectivity in temporo-parietal brain regions, phenotypes that are exacerbated in individuals with autism (Eagleson, Xie, & Levitt, 2017; Rudie et al., 2012). These functional changes associated with MET genotype are not surprising considering that MET signaling is involved in regulating dendritic growth, spine formation and excitatory (glutamatergic) synaptogenesis during early development (Peng et al., 2016).

It has been proposed that the inherent imbalances in synaptic connectivity observed in autism present a genetic substrate that increases susceptibility to environmental insults that impact neurodevelopmental processes that determine synaptic connectivity, such as neuronal migration, apoptosis, elaboration of axons and dendrites, and activity-dependent refinements of synaptic connections (Belmonte & Bourgeron, 2006; Stamou et al., 2013). Perturbations of the spatiotemporal patterns and/or magnitude or extent of any of these neurodevelopmental events can modify the patterning of neural networks in the developing brain to give rise to behavioral phenotypes associated with autism (Belmonte & Bourgeron, 2006; Lein, Silbergeld, Locke, & Goldberg, 2005). Research findings from studies of transgenic animal models that express autism risk genes further support the hypothesis that perturbations of dendritic growth, synapse formation and/or synapse stabilization result in altered patterns of synaptic connectivity that coincide with autism-relevant behavioral phenotypes (Bourgeron, 2009; Zoghbi & Bear, 2012). How environmental and genetic risk factors interact to influence autism risk and/or severity remains an outstanding question.

In this review, we discuss current hypotheses regarding mechanisms by which environmental chemicals interact with genetic susceptibility factors to modify autism risk. These mechanisms are illustrated in the context of polychlorinated biphenyls (PCBs), an extensively studied class of environmental contaminants for which there is scientific consensus that they alter normal neurodevelopmental trajectories in the human brain (Pessah, Lein, Seegal, & Sagiv, 2019).



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## 2. Environmental chemicals identified as putative autism risk factors

Early reports that *in utero* exposure to valproic acid or thalidomide during critical periods of development was associated with increased expression of autism-related traits in children (Rodier, Ingram, Tisdale, & Croog, 1997) raised significant interest regarding the role of chemical exposures in autism. Subsequent epidemiological studies reported an increased risk for autism associated with maternal use of various medications and drugs of abuse, including alcohol (Arndt, Stodgell, & Rodier, 2005; Christensen et al., 2013; Croen et al., 2011; Malm et al., 2012; Miller et al., 2005; Rodier et al., 1997; Rodier, Miller, & Brent, 2011), as well as prenatal or early postnatal exposure to diverse environmental chemicals. These

epidemiological studies, as well as preclinical studies, have identified structurally and mechanistically diverse environmental chemicals as putative autism risk factors. These include legacy contaminants well-established to interfere with normal neurodevelopment, such as lead, mercury, and polychlorinated biphenyls (PCBs), as well as more contemporary contaminants, such as pesticides (organophosphorus and organochlorine pesticides, neonicotinoids and pyrethroids), flame retardants (polybrominated diphenyl ethers or PBDEs), plasticizers (phthalates and bisphenol A or BPA), and complex environmental mixtures, notably air pollution (Carter & Blizard, 2016; Kalkbrenner et al., 2014; Landrigan et al., 2012; Masini et al., 2020; Pelch et al., 2019).

The epidemiologic evidence linking environmental chemical exposures and autism was reviewed in Kalkbrenner et al. (2014). These authors identified 58 relevant articles in the peer-reviewed literature published prior to March 1, 2014, of which 32 met their inclusion criteria (individual-level data on autism, exposure measures pertaining to pregnancy or the 1st year of life, valid comparison groups, control for confounders and adequate sample sizes). These 32 articles included studies of autism and estimates of exposure to tobacco, air pollutants, volatile organic compounds and solvents, metals, pesticides, PCBs, PBDEs, PFCs, BPA and phthalates. Many of these chemicals have been shown to cause neurodevelopmental effects in experimental animal or cell-based models that have face validity to behavioral outcomes or cellular phenotypes associated with autism (reviewed in Kalkbrenner et al., 2014; Stamou et al., 2013). Some of these environmental exposures also showed associations with autism in the analysis of the epidemiologic literature by Kalkbrenner and colleagues. The most strongly and consistently associated were traffic-related air pollutants, some metals and the organophosphorus and organochlorine pesticides, with suggestive trends for some volatile organic compounds and phthalates (Kalkbrenner et al., 2014). Interestingly, neither tobacco smoke, which has been strongly associated with increased ADHD risk (Polanska, Jurewicz, & Hanke, 2012), nor alcohol showed a consistent association with increased risk for autism. The authors of this analysis reached the broad conclusion that with the possible exception of studies of tobacco and alcohol, the relevant publications available at the time were too limited in scope to either infer causality or to rule out the possibility that these or additional environmental chemicals confer risk for autism.

A later scoping review of the human and animal research was published in 2018, which aimed to identify and categorize primary research and



reviews on the association between prenatal and early postnatal exposure to environmental chemicals and autism risk that were published through February 2018 (Pelch et al., 2019). Search criteria included studies that assessed exposure to environmental chemicals prior to 2 months of age in humans or 14 d in rodents and rodent studies that included at least one measurement of reciprocal social communicative behavior or repetitive and stereotyped behavior. The search identified 21,603 unique studies from which the authors selected 54 epidemiological studies, 46 experimental rodent studies, and 50 reviews as relevant. These studies covered 152 chemical exposures. The most frequently studied environmental chemicals in humans were particulate matter ( $n = 14$ ), mercury ( $n = 14$ ), nonspecific air pollution ( $n = 10$ ) and lead ( $n = 10$ ). Similarly, in rodents, mercury and lead were among the most studied environmental chemicals ( $n = 6$  and 4, respectively) along with the organophosphorus pesticide, chlorpyrifos ( $n = 9$ ). Similar to the conclusions reached by Kalkbrenner et al. (2014), Pelch et al. (2019) concluded that while research on this topic was rapidly expanding, the wide variability in study design and conduct, the exposures investigated and the outcomes assessed made it difficult to identify chemicals of concern, but based on the available literature, they recommended that chlorpyrifos, lead, and PCBs be systematically reviewed to assess their association with autism risk and severity.

A more recent narrative review of this literature published in 2020 (Cheroni, Caporale, & Testa, 2020) identified the following environmental chemicals as the most relevant in the context of autism risk: lead, methylmercury, air pollution, endocrine disruptors in general, phthalates, BPA, perfluoralkyl substances, and PCBs. In this review, we focus on the literature related to the association of PCBs with autism, but the reader is referred to recent reviews and meta-analysis of the literature regarding the association between autism phenotypes and either pesticides (Bertoletti et al., 2022; Maleki et al., 2022; Vester & Caudle, 2016) or air pollution (Cory-Slechta, Merrill, & Sobolewski, 2022; Fu, Guo, Cheung, & Yung, 2019; Yu et al., 2022).



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### **3. Mechanisms by which gene $\times$ environment interactions influence autism risk**

While it is now widely accepted that complex  $G \times E$  interactions influence the etiology of autism, the mechanisms by which genetic and environmental factors interact to influence individual autism risk and/or severity

remain speculative. Current hypotheses include (i) heritable deficits in xenobiotic metabolism, (ii) disruption of the gut microbiome, (iii) endocrine disruption, (iv) epigenetic alterations that alter gene expression, (v) inflammation and/or immune dysregulation, and (vi) convergence on signaling pathways that regulate brain development (Table 1). The scientific premise for each of these proposed mechanisms is briefly discussed in this section, with specific examples presented in subsequent sections focused on PCBs as putative autism risk factors. It is important to note that while there is evidence to support each of these G × E mechanisms in the determination of autism risk, at this time there is little evidence causally linking these mechanisms to autism. Establishing causality remains a significant goal of ongoing research.

### 3.1 Genetic polymorphisms in xenobiotic metabolism

Genetic mutations in enzymes that metabolize xenobiotics, including environmental chemicals, have been linked to increased autism risk (Mordaunt et al., 2019; Rossignol et al., 2014). In a genome-wide transcriptomic study of cord blood from autistic *vs.* neurotypical children, 172 genes were found to be differentially expressed between the two groups with several genes grouped into the “response to toxic substances” category (Mordaunt et al., 2019). The genes included those that encode members of the cytochrome P450 (CYP) family of enzymes, such as *CYP1A1*, that play critical roles in metabolizing diverse environmental chemicals (Nagai, Fukuno, Suzuki, & Konishi, 2016; Uwimana, Ruiz, Li, & Lehmler, 2019). Polymorphisms in CYP genes that influence CYP expression levels and/or activity have been shown to decrease detoxification of environmental chemicals or increase metabolic conversion of a non-toxic parent compound to a neurotoxic metabolite. Either functional consequence can effectively increase the neurotoxic potential of an environmental chemical.

Glutathione-dependent enzymes also play a key role in the detoxification of environmental chemicals, but this is not their only critical function: glutathione-mediated metabolism is critically important in maintaining intracellular redox homeostasis (Bjorklund et al., 2021; Liu, Tan, Song, & Song, 2020). Mothers who express genetic polymorphisms that decrease glutathione-mediated processes are at higher risk for having a child with autism, and these genetic polymorphisms occur with higher frequency in children with autism *vs.* neurotypical children (Rossignol et al., 2014). Consistent with these observations, glutathione S-transferase (GST)

**Table 1** Proposed mechanisms for how genetic and environmental factors interact to influence autism risk and severity.

<b>Mechanism</b>	<b>Rationale</b>	<b>References</b>
Heritable deficits in xenobiotic metabolism	Genetic mutations in enzymes that metabolize environmental chemicals have been linked to increased autism risk. A decreased ability to detoxify environmental chemicals or an increased effectiveness in converting benign parent compounds to neurotoxic metabolites might increase the neurotoxicity of an environmental chemical contaminant.	Bjorklund et al. (2021) Herbert (2010) Rock and Patisaul (2018)
Disruption of the gut microbiome	Clinical and experimental data indicate that the gut microbiome regulates neurodevelopment; the gut microbiota in children with autism differs from that of neurotypical children. Toxicological studies show that the gut microbiome influences xenobiotic metabolism and disposition, and, conversely, environmental chemicals can alter the gut microbiome.	Balaguer-Trias, Deepika, Schuhmacher, and Kumar (2022) Bertotto, Catron, and Tal (2020) Needham et al. (2022) Rosenfeld (2017) Vuong et al. (2020) Yousefi et al. (2022)
Endocrine disruption	Endocrine signaling, including signaling by thyroid hormones, sex steroids and glucocorticoids, critically modulates neurodevelopment. The incidence of autism exhibits a pronounced sex bias, with a male:female ratio of 4:1. Diverse environmental chemicals have been shown to alter endocrine signaling via various mechanisms.	Demeneix (2019) Moosa, Shu, Sarachana, and Hu (2018) Mari-Bauset et al. (2022) Ramirez et al. (2022) Weiss (2012)
Epigenetic mechanisms	Epigenetic mechanisms are critically important in regulating brain development. Environmental chemicals can alter DNA methylation, histone acetylation and miRNA expression profiles, and these parameters are altered in at least some children with autism.	Keil and Lein (2016) Kong, Zhou, and Sun (2020) Park, Lee, Kim, and Yi (2022) Parra and Johnston (2022)
Inflammation and/or immune dysregulation	Crosstalk between nervous and immune systems is essential for normal neurodevelopment, and environmental chemicals can trigger systemic and neuroinflammation as well as alter immune function. Clinical and experimental data confirm neuroinflammation and immune dysregulation in autism.	Arambula and McCarthy (2020) McLellan, Kim, Bruce, Ramirez-Celis, and Van de Water (2022) Meltzer and Van de Water (2017) Sotgiu et al. (2020)
Convergence of G × E on signaling pathways that regulate brain development	Many genetic risk factors for autism converge on several major signaling pathways that critically regulate synaptic connectivity in the developing brain. Environmental chemicals have been identified that target these same signaling pathways.	Ansel et al. (2016) Ebert and Greenberg (2013) Pourtavakoli and Ghafouri-Fard (2022) Purushotham et al. (2022) Stamou et al. (2013)

detoxification activity was found to be lower in children with autism *vs.* neurotypical controls (Serajee, Nabi, Zhong, & Huq, 2004). It was also recently shown that imbalances in the glutathione redox system contribute to the pathogenesis of autism via not only increased oxidative stress, but also altered E/I balance in the brain (Bjorklund et al., 2021). Glutathione is involved in regulating the N-methyl-D-aspartate (NMDA) receptor, which mediates signaling by glutamate, the primary excitatory neurotransmitter in the brain. Autism-linked deficits in glutathione-related regulation of glutamate have been linked to E/I imbalance in the brain, and in extreme cases, to excitotoxic cell death of neurons (Bjorklund et al., 2021).

### 3.2 Disruption of the gut microbiome

The metabolism of environmental chemicals is also influenced by the gut microbiome (Li, Tian, et al., 2022; Lim et al., 2020; Zimmermann, Zimmermann-Kogadeeva, Wegmann, & Goodman, 2019), and changes in the composition of the gut microbiome have been shown to alter the disposition and concentration of environmental chemicals throughout the body, including the brain (Li, Tian, et al., 2022). Conversely, environmental chemicals can alter the gut microbiome (Gama, Neves, & Pereira, 2022; Lai, Chung, Li, Wan, & Wong, 2016; Li, Hefti, Marek, et al., 2022; Rude, Keogh, & Gareau, 2019). Given clinical and experimental data indicating that the gut microbiome regulates neurodevelopment and central nervous system function (Alam, Abdolmaleky, & Zhou, 2017; Muller et al., 2020; Ristori et al., 2019), it is widely posited that interactions between environmental chemicals and the gut microbiome during critical stages of neurodevelopment may alter neurodevelopmental trajectories to confer risk for autism. This is supported by reports that the gut microbiota in children with autism differs from that of neurotypical children (Kang et al., 2017; Liu et al., 2019; Mayer, Padua, & Tillisch, 2014; Sharon et al., 2019). However, data demonstrating that environmental chemical interactions with the gut microbiome are causally related to increased expression of autism phenotypes is largely lacking. Carefully designed experimental animal studies and prospective clinical studies are needed to better understand whether certain gut microbiome compositions are more likely to lead to adverse effects from environmental chemical exposures and whether therapeutic interventions targeting the gut microbiome could be employed to mitigate autism risk associated with G × E interactions.

### 3.3 Endocrine disruption

Diverse environmental chemicals have been classified as endocrine disruptors because they interfere with endogenous endocrine signaling either by mimicking endogenous hormones or by decreasing the production, transport or signaling of endogenous hormones (Mari-Bauset et al., 2022; Salazar, Villaseca, Cisternas, & Inestrosa, 2021; Sechman, Batoryna, Antos, & Hrabia, 2016; Takeuchi et al., 2011; Weiss, 2012). Since endocrine signaling influences neural circuitry in the developing brain via modulation of neurodevelopmental processes that regulate neuronal connectivity (Demeneix, 2019; Moosa et al., 2018; Ramirez et al., 2022), it is widely posited that endocrine disrupting chemicals interact with genetic factors that regulate endocrine signaling to alter neurodevelopmental trajectories.

One endocrine signaling system thought to be targeted by diverse environmental chemicals to cause developmental neurotoxicity is the thyroid hormone (TH) system. TH signaling is critical for normal neurodevelopment (Demeneix, 2019), and congenital hypothyroidism, if untreated, causes severe adverse neurodevelopmental outcomes (Oppenheimer & Schwartz, 1997; Rovet, 2014; Williams, 2008). While conflicting, there is some evidence that TH insufficiency increases autism risk (Salazar et al., 2021), and genetic mutations in TH receptors have been observed in children with autism (Kalikiri, Mamidala, Rao, & Rajesh, 2017). A large number of environmental chemicals have been shown to decrease circulating levels of TH and/or to interfere with TH signaling at the level of the receptor (Salazar et al., 2021). While these observations collectively support the hypothesis that environmental chemicals confer autism risk via modulation of TH signaling, evidence of a causal link is lacking, as are data demonstrating that expression of genetic mutations in TH receptors increase susceptibility to the neurotoxicity of environmental thyroid hormone disruptors.

Another observation that has promoted the hypothesis of endocrine signaling as a mechanisms by which  $G \times E$  interactions confer autism risk is that autism disproportionately impacts males relative to females with a rate of diagnosis 3–4.5 times higher in males (Christensen et al., 2016; Zablotsky, Black, & Blumberg, 2017). This observation has led to the suggestion that sex steroids may be important in autism etiology. Sex steroid signaling determines the sexually dimorphic trajectories of brain development that produce sex differences in brain structure, synaptic connectivity and behavior (Collaer & Hines, 1995; McCarthy, 2016a, 2016b; McCarthy, Herold, & Stockman, 2018; Napolitano et al., 2022). Developmental surges

of fetal testicular testosterone, which is converted to 17 $\beta$ -estradiol in the brain, are responsible for masculinizing the brain, and environmental chemicals that interfere with this developmental event can alter neural circuitry (McCarthy et al., 2018; McCarthy, Arnold, Ball, Blaustein, & De Vries, 2012; Napolitano et al., 2022). There is evidence of differential brain expression of genetic variants of the androgen receptor in autism compared to age- and sex-matched controls (Henningsson et al., 2009). Postmortem analysis has revealed decreased abundance of estrogen receptors in the brain of individuals with autism (Crider, Thakkar, Ahmed, & Pillai, 2014). Thus, environmental chemicals could contribute to autism risk by altering the spatiotemporal profiles and/or levels of sex hormones or their receptors to disrupt the normal sex specific patterning and development of the brain.

### 3.4 Epigenetic mechanisms

Epigenetic mechanisms are critically important in regulating brain development. DNA methylation patterns, chromatin remodeling, and miRNA expression profiles can be altered by environmental chemicals, and changes in these epigenetic modifiers have been documented in individuals with autism (Keil & Lein, 2016; Tremblay & Jiang, 2019). Perhaps the strongest evidence supporting epigenetic mechanisms as a means by which environmental chemicals might influence autism risk comes from studies of the DNA methylation binding protein, methyl-CpG binding protein 2 (MeCP2). Mutations in MeCP2 cause Rett syndrome, which has a high comorbidity of autism diagnosis, and mutations in MeCP2 have been identified in autism independent of Rett syndrome (Cukier et al., 2012; LaSalle & Yasui, 2009; Percy, 2011; Wen et al., 2017). MeCP2 is a transcriptional repressor regulated by miR132 that regulates dendritic and synaptic morphogenesis and function (Klein et al., 2007). Mice that lack MeCP2 have reduced expression of GABRB3, a gamma-aminobutyric acid (GABA) receptor important in determining the balance between excitatory and inhibitory neurotransmission (Samaco, Hogart, & LaSalle, 2005). Altered methylation of MeCP2 in the cord blood of mothers has been correlated with environmental chemical exposures (Eguchi et al., 2019; Pilsner et al., 2009).

The microRNA, miR132, plays an important role in synaptogenesis and connectivity (Xu, Li, Ji et al., 2019). In mice, genetic deletion of miR132 impaired performance in learning and memory tasks, and either deletion or

overexpression of miR132 altered hippocampal transcription of genes related to synapse transmission, neuronal proliferation and learning and memory (Hansen et al., 2016). Brain levels of microRNAs have been reported to be elevated in autism (Abu-Elneel et al., 2008; Sarachana, Zhou, Chen, Manji, & Hu, 2010; Talebizadeh, Butler, & Theodoro, 2008), and environmental chemicals have been shown to alter brain expression of miR132 (Lesiak et al., 2014; Sima, Rossnerova, Simova, & Rossner Jr., 2021; Yu et al., 2021). Thus, microRNAs may represent a convergent target for genetic and environmental risk factors that alter synaptic connectivity.

There is evidence that epigenetic mechanisms influence xenobiotic metabolism. For example, comparative analyses of placental tissue from mothers who gave birth to a child later diagnosed with autism *vs.* placenta tissues from mothers whose children were neurotypical identified differentially methylated regions in a xenobiotic metabolism gene, *CYP2E1*, and the extent of differential methylation was further influenced by the mother's *CYP2E1* genotype (Zhu et al., 2019). Epigenetic mechanisms may also influence known genetic causes of autism. 15q11-q13 duplications are associated with a syndromic form of autism, and individuals with this duplication have lower levels of brain LINE-1 repetitive DNA methylation (Mitchell et al., 2012). The potential to alter gene expression across a wide array of genes important to neurodevelopment and neurotoxicity make epigenetic pathways a critical target of G × E interactions that modify autism risk and/or severity.

### 3.5 Inflammation and/or immune dysregulation

The immune system is inextricably linked with the central nervous system and plays a critical role in brain development and function (Ransohoff & Brown, 2012). For example, cytokines and microglia, the innate immune cells in brain, are necessary for establishing functional neural circuits in the developing brain, including those involved in social behavior (Deverman & Patterson, 2009; Garay & McAllister, 2010; Guedes, Ferreira, Costa, Cardoso, & Peca, 2022; Sullivan & Ciernia, 2022). While numerous cytokines have been implicated in modulating neurodevelopmental processes critical to determining synaptic connectivity, the proinflammatory cytokines interleukin (IL)-6 (Goines & Ashwood, 2013; Kummer, Zeidler, Kalpachidou, & Kress, 2021) and type II interferon, gamma (IFN $\gamma$ ) (Goines & Van de Water, 2010) are two key players. IL-6

is necessary for maintaining neural progenitor cells in mice (Bowen, Dempsey, & Vemuganti, 2011) and has been shown to promote neural differentiation in human induced pluripotent stem cells (Kummer et al., 2021; Xu et al., 2018). However, developmental timing is likely critical for these effects since IL-6 has also been reported to inhibit neural differentiation in hippocampal neurons from adult mice (Kong et al., 2019). IL-6 has also been reported to decrease dendrite number in cultured rat hippocampal neurons (Gadient, Lein, Higgins, & Patterson, 1998) and modulate dendrite growth in primary rat neurons in culture, promoting both dendrite retraction (Guo, Chandrasekaran, Lein, Kaplan, & Higgins, 1999) and increased dendrite number (Guo, Metzler-Northrup, Lein, Rueger, & Higgins, 1997) depending on cell type and culturing conditions. IL-6 also impacts synaptogenesis and connectivity, altering network activity in mouse hippocampal neurons, in part by reducing expression of glutamate receptors and calcium channel signaling (Vereyken, Bajova, Chow, de Graan, & Gruol, 2007). IFN $\gamma$  also regulates dendritic growth and synaptogenesis, causing dendritic retraction and impairing synapse formation in rodent sympathetic and hippocampal neurons (Kim, Beck, Lein, & Higgins, 2002; Vikman, Owe-Larsson, Brask, Kristensson, & Hill, 2001). IFN $\gamma$  can modulate synaptic activity in rat hippocampal neurons *in vitro*, causing marked increases in excitatory postsynaptic currents 48 h post exposure (Vikman et al., 2001). Similarly, microglia have been reported to play a critical role in regulating neural differentiation via engulfment of neural precursor cells and in pruning superfluous synapses in the developing brain (Guedes et al., 2022; Lebovitz, Ringel-Scaia, Allen, & Theus, 2018; Sullivan & Ciernia, 2022). Sex differences in microglial gene expression and function have been identified that play a key role in shaping sex-specific brain function and behavior. The levels of sex hormones, such as androgens, estrogens, and progesterone, vary in an age-dependent and sex-dependent manner, and microglia respond both directly and indirectly to changes in hormone levels by altering transcriptional gene expression, morphology, and function (Sullivan & Ciernia, 2022).

Human data support an association between the immune system and autism with a large body of evidence linking maternal or childhood infection with increased rates of autism (Krakowiak et al., 2017; Majerczyk, Ayad, Brewton, Saing, & Hart, 2022; Nielsen et al., 2022). A population-based study of children in Australia found that autoimmune disease in mothers or infection in children prior to age 2 were associated with increased odds of autism (Nielsen et al., 2022). Genetic studies have identified immune



system genes differentially expressed in individuals with autism *vs.* neurotypical controls, and transcriptomic studies reported that pathways involved in immune function were significantly associated with autism diagnosis (Ansel et al., 2016). In a population-based case control study of children in California, levels of IL-1 $\beta$  and IL-4 from neonatal blood spots were associated with increased odds of autism (Krakowiak et al., 2017). Further IL-6 and IFN $\gamma$  levels in mothers have been associated with elevated autism diagnosis in children (Majerczyk et al., 2022). Increased microglia cell activation has also been noted in postmortem analyses of brains from individuals with autism *vs.* neurotypical controls (Blagburn-Blanco, Chappell, De Biase, & DeNardo, 2022; Zhang, Wang, Li, Deng, & Shen, 2022). The role of the immune system in promoting masculinization of the brain likely provides a biological substrate for the sex bias in autism diagnosis among boys *vs.* girls (McCarthy, Nugent, & Lenz, 2017; McCarthy & Wright, 2017).

Given the importance of the immune system in establishing synaptic connectivity, and ample evidence that many environmental chemicals can disrupt immune function (Dietert, 2014; Eisner et al., 2022; Kreitinger, Beamer, & Shepherd, 2016; Winans, Humble, & Lawrence, 2011), it seems plausible that the immune system is a point of convergence for environmental and genetic factors to interact to confer risk for autism. However, as noted for other mechanisms of G  $\times$  E interactions, to date, there is no evidence causally linking environmental chemical and genetic effects on immune function to increased risk of autism.

### 3.6 Convergence of genes and environment on neurodevelopmental signaling pathways

Many genetic risk factors for autism converge on signaling pathways that critically regulate synaptic connectivity in the developing brain (Delorme et al., 2013; Guang et al., 2018; Landrigan et al., 2012; Masini et al., 2020; Qiu et al., 2012). Therefore, these signaling pathways and the neurodevelopmental processes regulated by these signaling pathways represent molecular and cellular points of convergence for environmental and genetic risk factors for autism (Table 2) (Stamou et al., 2013).

A number of genes identified as autism risk genes regulate dendritogenesis or synapse formation, elimination or stabilization. These include genes for neuroligins (*NLG3*, *NLG4*) (Sudhof, 2008; Zoghbi & Bear, 2012), neurexins (*NRXN1*, *NRXN3*) (Sciacca et al., 2022), and contactin-associated protein-2 (*CNTNAP2*) (Dennis et al., 2011; Scott-Van Zeeland

**Table 2** Autism-associated genes important for neuronal connectivity, dendritogenesis and synaptogenesis that may interact with environmental chemicals to increase autism risk.

Signaling pathway	Genes	References
Signaling pathways that regulate dendrite and/or synapse formation	<ul style="list-style-type: none"> <li>• Met Receptor Tyrosine Kinase (MET)</li> <li>• Neuroligins (NLG3, NLG4)</li> <li>• Neurexins (NRXN1, NRXN3)</li> <li>• Contactin-associated protein-2 (CNTNAP2)</li> <li>• SH3 and multiple ankyrin repeat domains 3 (SHANK3)</li> <li>• Extracellular signal-regulated kinase (ERK)</li> <li>• Phosphatidylinositol 3-kinases (PI3K)</li> <li>• Mammalian target of rapamycin (mTOR)</li> </ul>	<p>Chaudry and Vasudevan (2022)</p> <p>Dennis et al. (2011)</p> <p>Eagleson et al. (2017)</p> <p>Guang et al. (2018)</p> <p>Huang et al. (2019)</p> <p>Lutz et al. (2021)</p> <p>Rudie et al. (2012)</p> <p>Sciacca, Marino, Vitaliti, Falsaperla, and Marino (2022)</p> <p>Scott-Van Zeeland et al. (2010)</p> <p>Sudhof (2008)</p> <p>Wan et al. (2022)</p> <p>Zoghbi and Bear (2012)</p>
Convergence on calcium signaling pathways	<ul style="list-style-type: none"> <li>• cAMP response element-binding protein (CREB)</li> <li>• Wingless-type MMTV integration site family, member 2 (Wnt2)</li> <li>• Ryanodine receptors (RyRs)</li> <li>• Voltage gated calcium channels (CACNA family)</li> <li>• Voltage gated sodium channels (SCN family)</li> <li>• Ligand gated chloride channels (GABRB family)</li> <li>• Calcium activated potassium channels (KCNM family)</li> </ul>	<p>Deidda, Bozarth, and Cancedda (2014)</p> <p>Marcantoni, Calorio, Hidisoglu, Chiantia, and Carbone (2020)</p> <p>Nanou and Catterall (2018)</p> <p>Panesar, Kennedy, Keil Stietz, and Lein (2020)</p> <p>Schmunk and Gargus (2013)</p> <p>Skafidas et al. (2014)</p> <p>Soueid et al. (2016)</p> <p>Wayman et al. (2006)</p> <p>Wayman et al. (2012)</p> <p>Wayman et al. (2012)</p>

et al., 2010), all which have important roles in connecting and stabilizing presynaptic and postsynaptic components of the synapse. *CNTNAP2* mutations have been linked to increased autism risk, and expression of *CNTNAP2* gene variants are sufficient to alter connectivity in experimental models (Dennis et al., 2011; Scott-Van Zeeland et al., 2010). The SH3 and multiple ankyrin repeat domains 3 (*SHANK3*) gene has been identified as an autism risk gene (Huang et al., 2019; Lutz et al., 2021; Wan et al., 2022). *SHANK3* functions to interact with neuroligin and neurexin complexes to regulate activity-dependent synaptogenesis (Craig & Kang, 2007; Stamou et al., 2013). ERK, PI3K and mTOR signaling pathways are also strongly implicated in autism (Chaudry & Vasudevan, 2022; Lutz et al., 2021) and are important in regulating dendritic growth and synaptogenesis (Levitt & Campbell, 2009).

Neuronal activity plays a significant role in sculpting neural circuits in the developing brain, and calcium signaling is the major mechanism linking neuronal activity to dendritogenesis and synaptogenesis in the developing brain (Pessah, Cherednichenko, & Lein, 2010; Wayman et al., 2006). Thus, it is not surprising that genes that either control calcium signaling or are regulated by calcium signaling, are predominant in the list of autism risk genes (Ansel et al., 2016; Nanou & Catterall, 2018; Nguyen, Medvedeva, Ayyagari, Schmunk, & Gargus, 2018; Pessah et al., 2010). Diverse environmental chemicals have also been shown to disrupt these same calcium signaling pathways, suggesting a “two hit” mechanism in which genetic and environmental factors converge to alter the fidelity of calcium signaling resulting in altered synaptic connectivity (Keil Stietz et al., 2021; Klocke & Lein, 2020; Panesar et al., 2020; Stamou et al., 2013).

Evidence that neuronal calcium signaling is disrupted in autism also derives from phenotypes observed in syndromic disorders that have a high incidence of autism. For example, Fragile  $\times$  syndrome, which is caused by expansion of a CGG repeat ( $>200$ ) in the 5' non-coding portion of the fragile  $\times$  mental retardation 1 gene (*FMR1*), is the most prevalent single gene disorder associated with increased risk for autism (Krueger & Bear, 2011; Leehey & Hagerman, 2012). *FMR1* premutation (55–200 CGG repeats), which causes fragile X-associated tremor/ataxia syndrome marked by deficits in cognitive function, tremors and motor abilities in adults, is also associated with elevated risk of autism (Chonchaiya et al., 2012; Hagerman, Au, & Hagerman, 2011). Hippocampal neurons from *FMR1* premutation mice displayed elevated cytoplasmic calcium concentrations and abnormal glutamatergic responses *in vitro* (Berman, Murray, Arque, Hunsaker, & Wenzel, 2012; Chen et al., 2010; Robin et al., 2017).

FMR1 premutation mouse neurons also exhibited increased frequency and duration of clustered burst firing compared to wild type controls (Cao, Hulsizer, et al., 2012; Cao et al., 2013). FMR1 premutation neurons derived from human iPSC cells similarly displayed altered calcium signaling under baseline conditions and in response to glutamatergic stimulation (Liu et al., 2012). Since calcium signaling is a major driver of dendritic morphogenesis, it is not surprising that mice with FMR1 premutations also exhibited deficits in neuronal cytoarchitecture and learning and memory behavior (Berman et al., 2012; Chen et al., 2010; Diep et al., 2012; Keil et al., 2019; Sethi et al., 2021).

Dendrites can structurally remodel in response to environmental factors and experience. This structural plasticity is mediated by calcium signaling triggered by NMDA receptor activation that drives the sequential activation of calmodulin-dependent protein kinase kinase (CaMKK), CaMKI, and MAPK ERK/MEK ERK kinases to enhance cAMP response element-binding protein (CREB) resulting in Wnt2 transcription and dendritic growth (Wayman et al., 2006). CREB also regulates expression of miR132 during neuronal maturation and synaptogenesis (Hansen et al., 2013). CREB dysfunction is implicated in autism (Barnby et al., 2005; Ngounou Wetie et al., 2015; Todd & Mack, 2001; Zheng et al., 2016), and downstream genes such as miR132 and Wnt pathway members have also been linked to autism or autism-related phenotypes (Bocchi et al., 2017; Kalkman, 2012; Li et al., 2016). Environmental chemicals are also known to alter neurodevelopment via modulation of CREB dependent mechanisms (Connolly & Kingsbury, 2010; Jang et al., 2012; Sethi, Keil, & Lein, 2018).

Ryanodine receptors (RyRs) are important for regulating calcium release from the endoplasmic reticulum (Pessah et al., 2010). Point mutations in *RYR* are prevalent in the human population with ~35% of individuals carrying one or more *RYR* variants (Kim et al., 2013) that increase sensitivity to some anesthetics to trigger malignant hyperthermia (Pessah et al., 2010). Mice engineered to express human *RYR* mutations displayed enhanced sensitivity to inhaled anesthetics, and their neurons exhibited elevated intracellular calcium concentrations (Barrientos et al., 2012; Yuen et al., 2012). Neurons from *RYR* transgenic mice also exhibited altered dendrite arborization and deficits in behavioral tasks (Keil et al., 2019; Sethi et al., 2021). RyR2 mutations have been linked to autism (Soueid et al., 2016) and environmental chemicals have been shown to interact with genetic mutations in RyRs to influence dendritic arborization and behavior in mouse models (Keil Stietz et al., 2021; Sethi et al., 2021).

Genes that encode calcium ion channels other than RyRs, as well as channels that conduct ions other than calcium, have also been implicated in autism (Ansel et al., 2016; Nanou & Catterall, 2018; Schmunk & Gargus, 2013). These include the voltage-gated calcium channels (CACNA family), voltage-gated sodium channels (SCN family), ligand-gated chloride channels (GABRB family) and, more recently, calcium activated potassium channels (KCNM family) (Schmunk & Gargus, 2013). Mutations in the L-type calcium channel Ca(v)1.2 cause Timothy syndrome, which is associated with high rates of autism (Splawski et al., 2004). Mutations in Cav1.2 and Cav1.3 are also implicated as autism risk factors independent of Timothy syndrome (Marcantoni et al., 2020; Nanou & Catterall, 2018). Timothy syndrome is thought to cause autistic phenotypes via altered neuronal connectivity downstream of dysregulated calcium signaling (Nanou & Catterall, 2018). In neurons, this mutation elevated intracellular calcium levels and altered expression of genes regulated by calcium signaling, including CAMKII and CREB (Pasca et al., 2011). In a mouse model of Timothy syndrome, brains had reduced numbers of cortical projecting neurons, deficits in neuronal differentiation and elevated production of catecholamines, all of which are autism-relevant phenotypes (Pasca et al., 2011). Similarly, *de novo* mutations in voltage-gated sodium channels (SCN2A) are implicated as autism risk factors (Sanders et al., 2012). SCN2A are important in regulating action potentials and play an important role in synaptic plasticity (Spratt et al., 2019).

E/I imbalance is implicated in the pathogenesis of autism (Rubenstein & Merzenich, 2003), and this can result from structural changes in neural circuits and/or altered expression of receptors for excitatory *vs.* inhibitory neurotransmitters. For example, GABA receptor mutations are associated with increased autism risk (Deidda et al., 2014), and levels of GABRB3 were found to be lower in brains from children with autism compared to neurotypical controls (Samaco et al., 2005). *GABRB3* is located in the chromosome 15q11-13 locus, which is implicated in syndromic forms of autism and is thought to increase susceptibility to environmental insults (Mitchell et al., 2012; Shelton, Hertz-Picciotto, & Pessah, 2012).

KCNM channels are also important for regulating neuronal excitability, and KCNMA1 mutations that reduce activity of the channel have been observed in individuals with autism (Du et al., 2005; Laumonier et al., 2006; Schmunk & Gargus, 2013). KCNM channels have also been found to be regulated by Fragile  $\times$  mental retardation protein (FMRP) via a KCNMB4 regulatory subunit and loss of FMRP reduced channel activity,

which dysregulated neurotransmission (Deng et al., 2013). Mutations in the regulatory KCNMB4 subunit have been linked to autism, and KCNMB4 has been identified as one of the genes to be used in predictive panels of autism (Schmunk & Gargus, 2013; Skafidas et al., 2014).



#### 4. PCBs as putative autism risk factors

PCBs belong to a larger grouping of environmental contaminants referred to as persistent organic pollutants (POPs) that have in common environmental persistence and resistance to metabolic degradation. PCBs are a family of 209 structurally similar congeners that vary according to the number and position of chlorine substitutions on the biphenyl backbone (Klocke, Sethi, & Lein, 2019). PCBs are classically divided into two groups based on their structure and binding affinity for the aryl hydrocarbon receptor (AhR), which is the canonical receptor for dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD): coplanar, dioxin-like PCBs bind the AhR with moderate to high affinity, whereas the non-coplanar, non-dioxin-like (NDL) PCBs have little to no affinity for the AhR (Klocke et al., 2019). A subset of NDL PCBs have RyR activity (Holland et al., 2017; Pessah et al., 2019; Sethi et al., 2019). Some PCB congeners are reported to interact with steroid hormone receptors (Bell, Dryden, Will, & Gore, 2018; Bell, Hart, & Gore, 2016; Dickerson, Cunningham, Patisaul, Woller, & Gore, 2011; Sechman et al., 2016; Takeuchi et al., 2011; Takeuchi, Anezaki, & Kojima, 2017) and TH receptors (Itoh et al., 2018; Pessah et al., 2019; Salazar et al., 2021; Zoeller, 2007) and, thus, are postulated to cause developmental neurotoxicity via endocrine disruption (Bell et al., 2018; Walker, Goetz, & Gore, 2014; Winneke et al., 2014). The NDL PCBs are thought to have the most significant impact on neurodevelopmental outcomes (Klocke & Lein, 2020) and, therefore, are highlighted in this review.

Despite a ban on production of PCBs in the U.S. in the 1970s and globally in the early 2000s (Klocke et al., 2019; Melymuk et al., 2022), legacy PCBs produced prior to the ban persist in the environment to this day. Sources of legacy PCBs include leachate from waste sites, degradation of old building materials and release from PCB-containing fluorescent light ballasts, hydraulic equipment and capacitors still in use. In addition, there are contemporary sources of PCBs, including the unintentional production of PCBs as byproducts of the modern manufacturing processes used to

produce pigments found in paints, varnishes and caulking (Hannah, Megson, & Sandau, 2022; Herkert, Jahnke, & Hornbuckle, 2018; Hu & Hornbuckle, 2010; Liu et al., 2004), and the breakdown of higher chlorinated PCBs into lower chlorinated PCBs (Xiang, Xing, Liu, Qin, & Huang, 2020). Some of these contemporary PCBs were not present in the commercial mixtures produced prior to the ban, making contemporary PCB exposures unique compared to those that occurred prior to 1979. Understanding the neurotoxicological implications of PCBs not found in the legacy mixtures is an expanding area of research.

PCBs are ubiquitous contaminants readily detected in human tissues, livestock, fish, dairy products, water, soil, sediments and both indoor and outdoor air worldwide (Barmpas et al., 2019; Chen, Streifel, et al., 2017; Kania-Korwel & Lehmler, 2016; Li, Lim, et al., 2022; Sethi, Chen, Kass, & Puschner, 2017; Thompson & Boekelheide, 2013; Yu, Liu, Shu, Ma, & Pan, 2020). Because they are generally lipophilic, PCBs bioaccumulate up the food chain. Thus, humans are primarily exposed to PCBs via diet, although inhalation is becoming an increasingly important route of exposure, particularly to the lower chlorinated congeners (Ampleman et al., 2015; Carpenter, 2006; Chan-Hon-Tong, Charles, Forhan, Heude, & Sirot, 2013; Durand et al., 2008). In addition, PCBs cross the placenta and are present in breastmilk (Foerster et al., 2021; Kim et al., 2018). The National Health and Nutrition Examination Survey (NHANES) has documented widespread PCB exposure in women of child-bearing age in the U.S. (Thompson & Boekelheide, 2013). PCBs have been detected not only in serum of pregnant women but also in cord blood and brain tissue from young children (Baba et al., 2018; Eskenazi et al., 2017; Granillo et al., 2019; Hisada et al., 2014; Li, Lim, et al., 2022; Rosenquist et al., 2017). In one study, tissue levels of the NDL PCB congener, PCB 95, were found to be significantly higher in postmortem brain tissue from children with a genetic form of autism, 15q11-q13 duplication compared to neurotypical controls (Mitchell et al., 2012).

Reviews of the epidemiological evidence have almost universally concluded that the weight of evidence indicates that PCBs cause developmental neurotoxicity in humans; however, it is less clear whether PCBs are associated with increased risk for autism (Alampi et al., 2021; Bernardo et al., 2019; Lyall, Croen, Sjodin, et al., 2017; Mehri, Bashirian, Khazaei, & Jenabi, 2021; Pessah et al., 2019). For example, a recent narrative summary of the epidemiological literature published between 1990–2018 identified 29 peer-reviewed publications that fit

inclusion criteria for sample size (>100), measurement of prenatal PCB levels in biological samples collected during pregnancy or delivery, and behavioral assessment of children at 3 years old or older (Pessah et al., 2019). The studies included in the analysis examined diverse cohorts from across North America, Asia, and Europe. The review identified 12 publications from 9 different cohorts that examined impacts of PCBs on cognitive function among children aged 3–11 years. Of these, most (8 of 12) found positive associations between PCB exposure and cognitive or language deficits in children (Pessah et al., 2019). A total of 17 studies from 11 different cohorts examined associations of prenatal PCBs with attention, behavioral regulation and social behavior among 3–12-year-old children (Pessah et al., 2019). The majority (10 of 17) reported PCB-related associations with impulse control, hyperactivity, and attention. Only two of the 17 studies examined PCBs in relation to social behavior and autistic traits, with one study reporting that total PCB levels were associated with fewer autistic traits (Nowack, Wittsiepe, Kasper-Sonnenberg, Wilhelm, & Scholmerich, 2015) and the other reporting congener-specific associations with autistic traits (Braun et al., 2014).

As acknowledged by the authors (Pessah et al., 2019), a limitation of the studies included in their review was that associations with specific PCB congeners or mechanism-based classes of congeners were not evaluated largely because most epidemiologic studies report total sum PCB levels or levels of “indicator” PCBs in biological samples. The significance of this limitation is underscored by a recent study suggesting that NDL PCBs with activity at the RyR, but not dioxin-like PCBs or total PCBs, are positively associated with autism (Granillo et al., 2019). The genetic substrate likely also influences the impact of PCBs on autism-relevant outcomes, as illustrated by a recent pilot study not included in this review that identified a trend towards a positive association between PCB 153 and autism in individuals with a deletion mutation in the gene encoding glutathione transferase but not in individuals who did not have this mutation (Bach et al., 2020). Also not included in the summary, because the age of the child at the time of autism diagnosis was not specified, was a 2017 study that found a positive association between PCB exposure and autism (Lyall, Croen, Sjodin, et al., 2017). Furthermore, a 2020 study reported an association between plasma PCB concentrations measured during pregnancy and increased incidence of autistic behaviors in children aged 3–4 years old when the data were analyzed using Bayesian predictive odds ratios (Bernardo et al., 2019). When considering these additional studies that have examined the



impact of prenatal PCB on autism phenotypes together with the studies included in the review, most (five of six) report that PCBs increase the expression of autistic traits.

More recently, a meta-analysis was conducted of studies published through 2019 that reported odds ratios for PCB exposure and autism from case-control or cross-sectional studies (Mehri et al., 2021). The authors used random-effects models to examine the association among five different studies representing five independent cohorts from across North America and Finland using pooled odds ratios (ORs) and their 95% confidence intervals (CI). The pooled ORs indicated a significant association between PCB exposure during pregnancy and autism risk (OR, 1.80; 95% CI, 1.26–2.34) (Mehri et al., 2021). One of the studies included in the meta-analysis was a study from 546 mothers and infants in Canada that found children age 3–4 had increased social responsiveness scale (SRS) scores and increased odds of more autistic behavior in the highest plasma PCB concentration (sum of 24 PCB congeners) during pregnancy groups compared to the lowest PCB groups (Bernardo et al., 2019). A new study has since been conducted using the same cohort of 478 Canadian mothers and children but applying different regression models and found the sum of 4 PCBs (PCB 118, PCB 138, PCB 153 and PCB 180) was also associated with higher SRS scores (Alampi et al., 2021). These four PCBs were also identified in another study (Lyall, Croen, Sjodin, et al., 2017) included in the Mehri et al., 2021 meta-analysis that linked prenatal PCB exposure to autism risk. In a California cohort of 545 children with autism, mean levels of prenatal PCBs were higher in this group compared to general population controls, and autism risk was most elevated in the highest *vs.* lowest quartiles of prenatal PCB levels. Associated risk was especially prevalent for several individual congeners, including PCB 138/158, PCB 153, PCB 170 and PCB 180 that all had odds ratios of  $\sim 1.5$  (Lyall, Croen, Sjodin, et al., 2017). Observations that specific congeners can differentially influence neurodevelopmental outcomes is an area of future study. This is particularly important given mechanistic data indicating that different subgroups of PCBs have different molecular targets (Klocke et al., 2019; Klocke & Lein, 2020). The implications are illustrated by the findings of a previously mentioned study of 104 mother-child pairs that found while total sum PCB levels were not associated with an increased risk of autism, prenatal levels of RyR-active congeners were linked to increased autism risk (Granillo et al., 2019). Thus, it is important to examine PCB links to autism phenotypes based on PCB structure and toxicological activity.

Clearly, these studies suggest that PCBs *per se* are not causing autism, but rather that PCBs increase risk for autism, likely by interacting with genetic susceptibilities. The questions then are which genes are PCBs interacting with to confer autism risk, and what are the mechanism(s) underlying G × PCB interactions? In a study of 206 autism susceptibility genes to determine which were targeted by chemicals included in the Comparative Toxicogenomics Database (CTD), over 1 million interactions were found with PCBs representing one of the major chemical classes of concern found to interact with autism risk genes (Carter & Blizard, 2016). In this study, the top three PCBs, PCB 153, PCB 138 and PCB 126, were found to affect a total 419, 569, and 1243 genes, respectively, and within those affected genes, 22, 20 and 24 were grouped as autism risk genes, respectively (Carter & Blizard, 2016). Below, we summarize the current literature related to how PCBs may interact with genetic risk factors to confer autism risk.

#### 4.1 PCB interactions with xenobiotic metabolism

PCBs are metabolized by CYP enzymes, including *Cyp1a1* (Grimm et al., 2015; Liu et al., 2020). *Cyp1a1* is a transcriptional target of the AhR that is upregulated in the liver by PCB exposure in rodent models (Chubb et al., 2004), and the extent of *Cyp1a1* induction following PCB exposure is influenced by the gut microbiome (Lim et al., 2020). A transcriptomic study found that *CYP1A1* was downregulated in cord blood from individuals with autism *vs.* neurotypical controls, which would be predicted to decrease the rate and/or extent of PCB metabolism (Mordaunt et al., 2019; Thony, Auerbach, & Blau, 2000). This suggests that the population with autism, or at least a subgroup with decreased *CYP1A1* expression, may be more susceptible to PCB effects on neurodevelopment compared to neurotypical controls.

Glutathione-mediated transformation is another major route of PCB detoxification (Mandic-Maravic et al., 2019; Matelski & Van de Water, 2016). Glutathione S-transferase (GST) activity was found to be lower in children with autism *vs.* neurotypical controls (Serajee et al., 2004). In addition, genetic polymorphisms in the glutathione pathway were detected at a higher frequency in autism *vs.* typically developing children, and mothers who expressed these genetic polymorphisms were at higher risk for having a child diagnosed with autism (Rossignol et al., 2014). Importantly, GST genotypes have been shown to influence PCB concentrations in children with autism (Amen et al., 2022). In a study of 125 children from Pakistan

with autism, blood concentrations of PCB 77, PCB 118, PCB 128 and PCB 153 were significantly higher in autism cases compared to neurotypical controls (Amen et al., 2022). Conversely, PCB 187 was higher in control blood than autism cases, while other PCB congeners analyzed were not different between populations (Amen et al., 2022). This study also examined the impact on PCB levels of expression of genetic polymorphisms in the glutathione transferase gene, *GSTT1*. PCB 66 and PCB 156 concentrations were higher, while PCB 81 and PCB 118 were lower in the *GSTT1* null genotype compared to the “wildtype” *GSTT1* genotype. Among the autism cases, PCB 44 and PCB 128 concentrations were higher, while PCB 167 was lower in null *vs.* wildtype *GSTT1* genotypes. Similar differences in PCB accumulation were also noted for another glutathione genotype, *GSTM1* (Amen et al., 2022). These findings highlight the role that xenobiotic metabolism may play in determining the PCB profile present in the brain of exposed individuals. Moreover, this study clearly demonstrates that genotypic variations in glutathione genes influence autism risk, underscoring the challenge of conducting epidemiological studies with sufficient power to study causal relationships between PCB exposures and autism risk.

PCB metabolism is also important to consider in light of emerging data that PCB metabolites can have detrimental effects on the central nervous system (Berghuis, Soechitram, Hitzert, Sauer, & Bos, 2013; Dreiem, Rykken, Lehmler, Robertson, & Fonnum, 2009; Hisada et al., 2014; Nomiyama et al., 2019; Sethi, Keil, et al., 2017; Takeuchi et al., 2011; Tehrani & Van Aken, 2014; Uwimana et al., 2019) and that hydroxylated PCB metabolites are detected in human brain samples (Li, Lim, et al., 2022). Hydroxylated metabolites of some PCB congeners inhibited TH-dependent dendritic growth in cultured rodent Purkinje neurons (Kimura-Kuroda, Nagata, & Kuroda, 2005, 2007), while other hydroxylated PCB metabolites induced TH-independent dendritic growth in Purkinje neurons (Kimura-Kuroda et al., 2007). PCB 11 and its hydroxylated and sulfated metabolites enhanced rat hippocampal and cortical dendritic and axonal complexity *in vitro*, although the sulfated metabolites were more potent than the parent compound (Sethi, Keil, et al., 2017). PCBs have also been shown to trigger apoptosis of hippocampal neurons *in vitro* and *in vivo* via oxidative stress (Howard, Fitzpatrick, Pessah, Kostyniak, & Lein, 2003; Yang & Lein, 2010), and hydroxylated PCB metabolites similarly induced apoptosis of cultured rat cerebellar granule cells via oxidative stress, in part through a mechanism involving ERK1/2 signaling (Dreiem et al., 2009). Thus, while the ultimate purpose of PCB

metabolism is to facilitate elimination of PCBs from the body, the metabolites appear to have deleterious effects on critical neurodevelopmental processes implicated in the pathogenesis of autism. Moreover, these observations support the hypothesis that heritable deficits in metabolic pathways can exacerbate the developmental neurotoxicity of PCBs.

## 4.2 PCB interactions with the gut microbiome

Exposure to PCBs has recently been demonstrated to alter the gut microbiome in mice exposed throughout gestation and lactation to PCBs in the maternal diet. Specifically, in offspring exposed developmentally to the MARBLES (Markers of Autism Risk in Babies—Learning Early Signs) PCB mixture, which simulates the relative proportions of the twelve most abundant PCB congeners found in the serum of pregnant women living in Northern California who are at increased risk for having a child with autism (Hertz-Picciotto, Schmidt, et al., 2018), the beta diversity of the gut microbiome was significantly altered compared to vehicle controls (Rude et al., 2019). This change was further exacerbated by expression of heritable human mutations in genes that alter the fidelity of calcium signaling (CGG premutation plus gain-of-function RyR mutation) (Rude, Keogh, & Gareau, 2019). Adult mice exposed to PCBs were found to have altered gut microbiota characterized by changed alpha diversity and reduced beneficial bacteria, and these effects were exacerbated when combined with a high fat diet (Chi et al., 2018; Petriello, Hoffman, Vsevolozhskaya, Morris, & Hennig, 2018; Wahlang et al., 2021). Recently, it was demonstrated that not only does PCB exposure alter the gut microbiome, but also that the gut microbiome influences PCB metabolism and disposition. Thus, tissue levels of PCBs were higher in conventional mice with a normal microbiome than in germ-free mice that lack a microbiome following comparable PCB exposures (Li, Tian, et al., 2022). The gut microbiome also altered the gut–liver axis as evidenced by differential patterns of gene expression in the liver of conventional *vs.* germ-free mice following exposure to a human-relevant PCB mixture (Lim et al., 2020). Genes that were differentially regulated included *Cyp* genes and other genes involved in PCB metabolism. These findings revealed significant interplay between PCB exposures and the microbiome with the microbiome influencing neurotoxic responses and PCBs influencing microbial diversity in the gut. Whether and how these interactions influence autism risk and/or severity represent an intriguing area of future study.

### 4.3 PCBs as endocrine disruptors

PCBs have been shown to disrupt endocrine signaling via diverse mechanisms. In humans, PCB levels were reported to be inversely correlated with testosterone levels in adults (Goncharov et al., 2009), and maternal serum PCB levels were linked to altered testosterone and estradiol levels in cord blood of female and male newborns (Cao et al., 2008). PCB levels in maternal serum were also associated with changes in sex-typical behaviors in children age 6–8, generally increasing feminine scores in boys and decreasing feminine scores in girls (Winneke et al., 2014). In rats, developmental exposure to an estrogenic PCB mixture (the commercial mixture Aroclor 1221) changed the sexual differentiation of the adult brain, most notably causing masculinization or defeminization of the female brain (Dickerson et al., 2011; Walker et al., 2014). Thus, PCBs appear capable of influencing steroid hormone levels or signaling pathways, but whether these endocrine effects are causally linked to PCB effects on autism-relevant phenotypes is unknown.

Multiple animal studies have demonstrated that PCB exposures can decrease serum TH levels in pregnant dams and disrupt TH homeostasis in dams and offspring via effects on TH synthesis, transport, and metabolism (Zoeller, 2007). While similar relationships between PCBs and serum TH levels have been reported in humans, recent epidemiologic studies (Itoh et al., 2018) suggest that this may not be a consistent relationship in humans. Early experimental studies demonstrated a causal link between PCB-mediated decreases in serum TH levels and neurotoxic effects. Specifically, TH supplementation prevented motor and auditory deficits induced by developmental exposure to Aroclor 1254 in rats (Goldey & Crofton, 1998) and reversed PCB effects on oligodendrocyte maturation and myelination *in vitro* (Nave & Werner, 2014), both phenotypes associated with autism (Lord et al., 2018). However, experimental animal studies suggest that the cognitive deficits associated with developmental PCB exposure occur independent of decreased serum TH levels. For example, developmental exposures of rats to Aroclor 1254 at levels that significantly reduced maternal serum TH levels were not associated with learning and memory deficits or changes in neuronal progenitor cell proliferation and survival in exposed offspring (Zahalka, Ellis, Goldey, Stanton, & Lau, 2001). Conversely, developmental exposure to Aroclor 1254 at lower levels that did not significantly decrease serum TH levels caused significant performance deficits in the Morris water maze (Yang et al., 2009). Studies with individual PCB congeners also provide little support for the hypothesis that TH deficits mediate the cognitive effects of PCBs. For example, the NDL

PCBs 28, 118 and 153 produced similar deficits in spatial learning and memory, but their effects on serum T4 levels varied from a marked reduction to no effect. In contrast, DL PCBs 77 and 126 significantly reduced serum TH, but had few, if any, adverse effects on cognitive behavior (reviewed in [Pessah et al., 2019](#)). The inconsistencies observed across both human and rodent studies raise significant questions regarding a causal association between PCB effects on serum TH levels and cognitive behaviors. Fewer studies have focused on the effects of PCBs on sociability and repetitive behavior in rodent models (reviewed in [Klocke & Lein, 2020](#)). However, one study reported that developmental exposure to the MARBLES PCB mixture on behavioral phenotypes in mice were observed independent of altered serum TH levels ([Sethi et al., 2021](#)).

Alternatively, it has been proposed that the developmental neurotoxicity of PCBs is mediated by PCB interactions with TH receptors and/or the transcriptional machinery that regulates expression of TH-responsive genes. Early evidence in support of this hypothesis derived from a study showing that gestational exposure of rats to Aroclor 1254 in the maternal diet increased expression of TH-responsive genes in the fetal cortex despite significantly reducing maternal levels of serum TH, suggesting direct effects of PCBs on TH receptors in the fetal brain (reviewed in [Zoeller, 2007](#)). However, recent *in vitro* studies of PCBs abundant in the serum of pregnant women at increased risk for having a child diagnosed with autism found no significant agonistic or antagonistic interactions with canonical TH receptors expressed in a TH reporter cell line when exposed to these PCBs singly or in combination over a wide range of concentrations ([Sethi et al., 2019](#)). This same study also saw no effect of human-relevant hydroxylated or sulfated metabolites of PCB 11 and PCB 52 on TH receptor activity. These observations are consistent with an earlier study that failed to detect a direct interaction between Aroclor 1254 and TH receptors ([Zoeller, 2007](#)). The lack of convincing evidence demonstrating direct molecular interactions of PCBs with TH receptors has led to suggestions that PCBs may affect TH signaling via modulation of crosstalk between TH and other endocrine hormones and nuclear receptors ([Kouidhi & Clerget-Froidevaux, 2018](#)). However, to date, there are no experimental data directly linking PCB effects on TH signaling to effects of developmental PCB exposure on cognitive, social or repetitive behaviors. In contrast, evidence of causal relationships between PCB effects on serum TH levels and auditory and motor deficits and myelination suggest the possibility that interactions between PCBs and TH signaling may contribute to a subset of autism phenotypes.

#### 4.4 Epigenetic effects of PCBs

*In vitro* and *in vivo* models have demonstrated that PCBs can alter epigenetic endpoints relevant to autism. One major target includes the family of genes responsible for maintaining or adding DNA methylation marks, the DNA methyltransferases (*Dnmts*) (Feng et al., 2010; Keil & Lein, 2016; Okano, Bell, Haber, & Li, 1999). PCB 153 decreased DNA methyltransferase activity in cultured embryos (Wu, Zhou, & Ohsako, 2006), a mixture of 15 PCBs reduced expression of *Dnmts* and methyl donor S-adenosylmethionine in the liver of developmentally exposed rats (Desaulniers et al., 2009), and developmental exposure to Aroclor 1221 increased *Dnmt* abundance in sexually dimorphic regions of the rat brain (Walker et al., 2014). These observations suggest that PCB effects on *Dnmt* expression and activity vary depending upon the timing of exposure, the PCB congeners and doses to which the system is exposed, and the target tissue. Evidence also suggests that PCBs alter global DNA methylation levels in the brain following developmental exposure. In a mouse model, developmental exposure to the MARBLES PCB mix caused significant brain hypermethylation compared to vehicle control, an effect unique to male offspring (Laufer et al., 2022). In addition to global changes, developmental exposure to the MARBLES PCB mix also resulted in differentially methylated genes within the brain and placenta of mouse offspring (Laufer et al., 2022). Several of the differentially methylated genes have been linked to PCB-induced developmental neurotoxicity, such as Wnt and calcium signaling molecules, as well as MeCP2 mutations associated with Rett syndrome and autism (Chen et al., 2015; Laufer et al., 2022).

These studies illustrate that PCBs can change DNA methylation in genes relevant to autism and are consistent with epidemiological evidence that PCB exposures are linked to alterations in the epigenome. For example, in a study of 399 Japanese women, serum levels of NDL PCBs were inversely associated with global DNA methylation levels in peripheral leukocytes (Itoh et al., 2014), which is similar to findings in another study of 89 Koreans (Kim et al., 2010) and 70 Greenlandic Inuit Indians (Rusiecki et al., 2008). Others have found levels of dioxin-like PCBs are associated with global DNA hypermethylation (Lind et al., 2013); thus, differences in PCB exposures with respect to congener profiles and levels and timing of exposure likely alter the influence of PCBs on the epigenetic landscape and make epidemiological studies extremely challenging. In addition to global changes, gene specific alterations have also been observed in humans exposed to PCBs. For example, altered methylation of MeCP2 in the cord

blood of Japanese infants is correlated with environmental exposure to PCBs (Eguchi et al., 2019). Epigenetic mechanisms may also influence other known genetic causes of autism. For example, 15q11-q13 duplications are associated with a syndromic form of autism, and individuals with this duplication have lower levels of brain LINE-1 repetitive DNA methylation (Mitchell et al., 2012). Interestingly, these same individuals had higher levels of PCB 95 than typically developing controls, and this genetic mutation was the strongest predictor of PCB 95 levels (Mitchell et al., 2012). Considering the important role for epigenetic mechanisms in normal neurodevelopment and the epigenetic disruptions noted in autism, epigenetic modifications provide a convergent target by which PCBs may influence autism risk.

#### 4.5 PCB effects on the immune system

Numerous studies in humans and both *in vivo* and *in vitro* experimental models have demonstrated that PCBs can modulate immune function (Kramer, Hikel, Adams, Hinds, & Moon, 2012; Liu, Lu, Zhong, Wang, & Xu, 2022). For example, it has been reported that developmental PCB exposures suppressed immune responses to diverse vaccines in children in Norway (Hochstenbach et al., 2012), the Netherlands (Stolevik et al., 2013; Weisglas-Kuperus et al., 2000), the Faroe Islands (Heilmann et al., 2010), Sweden (Glynn et al., 2008), and in Inuit infants from Nunavik, Quebec (Dallaire et al., 2004). In the Norwegian cohort, the immunosuppressive effects of PCBs coincided with transcriptional changes of several genes in cord blood related to immune function (Hochstenbach et al., 2012), and with increased infections (Stolevik et al., 2011). These associations are likely influenced by specific PCB congeners since increased rates of childhood infection in Swedish children were observed for PCB 28, PCB 52 and PCB 101, but not for other *mono-* and *di-ortho* substituted PCBs (Glynn et al., 2008). In mononuclear cells cultured from cord blood collected from children in Canada with relatively elevated PCB exposures via high dietary intake of PCB-contaminated fish, release of the proinflammatory cytokine tumor necrosis factor alpha (TNF $\alpha$ ) was inversely associated with umbilical cord blood concentrations of PCBs (Bilrha et al., 2003). Gene expression analysis of human peripheral blood mononuclear cells incubated with various PCBs revealed differentially regulated gene expression in the presence of dioxin-like and NDL PCBs, with dioxin-like PCBs eliciting a greater number of changes



(Leijs et al., 2019). Genes that were downregulated were predominately those involved in immune response (Leijs et al., 2019). Rodent studies further strengthen the association of PCBs with altered immune/inflammation responses. In pregnant rats, exposure to Aroclor 1254 increased expression of IL-6, IFN $\gamma$  and IL-2 in liver and serum (Xu, Guo, Li, Pan, & Ma, 2019). In another rat study, developmental exposure to PCB 126 via the dam increased IL-1B and IFN $\gamma$  in the serum of offspring (Ahmed, El-Gareib, & Shaker, 2018). Similarly, gestational exposure to Aroclor mixtures via the maternal diet resulted in differential cytokine expression within the brain of rat offspring and further exacerbated serum cytokine IL-1 $\beta$  and IL-6 increases upon challenge with the inflammatory agent, lipopolysaccharide (LPS) (Bell et al., 2018). The findings in rodent models are consistent with the epidemiological observations (Dietert, 2014).

G  $\times$  E interaction studies in rodent models have been conducted to better understand the convergence between PCBs and autism risk genes on the immune response. The impact of developmental exposure to the MARBLES PCB mixture on brain and serum cytokine levels was quantified in mice engineered to express genetic mutations that alter the fidelity of calcium signaling (Keil et al., 2019), e.g., a RyR gain-of-function mutation and/or CGG premutation repeat expansions in the *FMR1* gene (Matelski et al., 2020). Mutations in *RYR1* and *FMR1* are both linked to dysregulated calcium signaling and confer heightened sensitivity to environmental stressors in multiple cell types from mice (Barrientos et al., 2012; Cao et al., 2012, 2013) and affect immune function in humans and mice (Careaga et al., 2014; Marek et al., 2012; Vukcevic et al., 2013). Dose-dependent effects of PCB exposure on cytokine concentrations were observed in the serum, but not hippocampus, with 13 of 23 serum cytokines increased by PCB exposure. Differential effects of genotype were observed in the serum and hippocampus. Hippocampal cytokines were consistently elevated in RyR mutant mice and also in wildtype animals for some cytokines compared to CGG premutation and double mutant mice, while serum cytokines were mostly elevated in the mutant genotypes compared to the wildtype group. Males had elevated levels of 19 cytokines in the serum and 4 in the hippocampus compared to females, but there were also interactions between sex and genotype for 7 hippocampal cytokines. Only serum levels of the chemokine CCL5 showed an interaction between PCB dose, genotype, and sex. Serum levels of CCL5 generally increased with increasing PCB dose, and this effect was exacerbated in the mutant mouse models (Matelski et al., 2020).

These observations support the hypothesis that the genetic substrate influences PCB effects on cytokine expression. However, it remains unknown whether these interactions are causally related to autism risk. Another notable data gap is the effects of PCBs on microglia. Given the critical role that microglia play in sculpting neural circuitry in the developing brain (Sullivan & Ciernia, 2022), this would appear to be an important question that warrants investigation.

#### 4.6 PCB interactions with genes that regulate calcium-dependent signaling

PCBs have been shown to modulate signaling pathways important for regulating dendritic arborization, synaptogenesis and synaptic connectivity (Klocke et al., 2019; Klocke & Lein, 2020). Dendritic morphology is a critical determinant of synaptic connectivity and changes in dendritic morphology (increased or decreased dendrite number, branching and/or spine density) contribute to the altered patterns of neuronal connectivity observed in many neurodevelopmental disorders, including autism (Alaerts et al., 2016; Cooper et al., 2017; Coskun, Loveland, Pearson, Papanicolaou, & Sheth, 2013; Keown et al., 2013; Khan et al., 2015). Various NDL PCBs have been shown to promote dendritic arborization and spine formation in hippocampal and cortical neurons both *in vitro* and *in vivo* (Keil, Sethi, & Lein, 2018; Keil Stietz et al., 2021; Lesiak et al., 2014; Sethi et al., 2018; Wayman, Yang, et al., 2012; Yang et al., 2009, 2014). These morphometric effects of NDL PCBs are largely mediated by calcium-dependent signaling pathways (reviewed in Panesar et al., 2020). Several NDL PCBs, exemplified by PCB 95 and PCB 136, trigger calcium signaling pathways via interactions with RyRs that enhance the open probability of these calcium ion channels embedded in the membrane of the endoplasmic reticulum, which effectively increases intracellular calcium concentrations (Pessah et al., 2010; Wayman, Bose, et al., 2012). These effects of PCB 95 and PCB 136 on RyR activity (Wayman, Yang, et al., 2012; Yang et al., 2014) trigger calcium-dependent signaling pathways, which in turn activate CREB-dependent transcriptional mechanisms (Lesiak et al., 2014; Wayman, Bose, et al., 2012) and mTOR-dependent translational mechanisms (Keil, Miller, Chen, et al., 2018) to stimulate dendritic growth and spine formation. The dendrite promoting effects of PCB 95 and 136 were blocked by pharmacological antagonism or siRNA knockdown of RyRs. PCB 66, a congener with physicochemical properties comparable to that of PCB 95 that lacks RyR activity, did not promote dendritic growth

or spine formation (Lesiak et al., 2014; Wayman, Bose, et al., 2012; Yang et al., 2014). Interestingly, point mutations in the RyR that increase the sensitivity of these ion channels to PCB 95 in animal models (Kim et al., 2013; Ta & Pessah, 2007) have been identified in autism candidate gene studies (Lu & Cantor, 2012). Collectively, these observations suggest that RyRs represent a convergent target for  $G \times PCB$  interactions that confer autism risk.

While PCB 95 and PCB 136 were found to enhance dendritic arborization via RyR-dependent mechanisms that converged on CREB-mediated transcription (Wayman, Bose, et al., 2012), a lower chlorinated contemporary PCB of concern, PCB 11, also has been found to promote dendritic growth in cultured hippocampal and cortical neurons via CREB-dependent mechanisms (Sethi et al., 2018) despite having negligible RyR activity (Sethi et al., 2019). The upstream calcium signaling molecules that link PCB 11 to CREB activation are as yet unknown. CREB dysfunction has been observed in autism (Barnby et al., 2005; Ngounou Wetie et al., 2015; Russo, Albert, & Bowman, 2017; Todd & Mack, 2001; Zheng et al., 2016), suggesting that heritable deficits in CREB signaling may be a more universal convergent target than RyRs in  $G \times PCB$  interactions that increase autism risk.

PCB effects on dendritic growth have been demonstrated to coincide with autism-relevant behavioral phenotypes. Gestational and lactational exposure to Aroclor 1254 at 1 or 6 mg/kg/d (Yang et al., 2009) or to PCB 95 at 0.1, 1, but not 6, mg/kg/d (Wayman, Yang, et al., 2012) in the diet of rat dams increased dendritic complexity of pyramidal neurons in the hippocampus, cortex and cerebellum of offspring not subjected to training in the Morris Water maze. Experience-dependent dendritic growth associated with Morris water maze training was significantly diminished or even blocked in animals developmentally exposed to PCBs (Yang et al., 2009). PCB restriction of experience-dependent dendritic growth was associated with deficits in spatial learning and memory (Yang et al., 2009). Developmental exposure to PCB 95 also interfered with the synaptic plasticity and organization of the auditory cortex in rats, causing significant E/I imbalance (Kenet, Froemke, Schreiner, Pessah, & Merzenich, 2007). Establishing that RyR-dependent effects of PCBs on dendritic growth and synaptic plasticity are causally related to PCB effects on behavior is difficult since pharmacological or genetic deletion of RyR is embryolethal and in postnatal animals, cardiotoxic. However, a recent study using a larval zebrafish model to compare behavioral phenotypes following

developmental exposures to PCBs with varying RyR activity ranging from little to very potent activity demonstrated that the structure–activity relationship (SAR) for RyR activity in zebrafish tissues predicted the SAR for PCB effects on behavior (Yaghoobi et al., 2022). This finding, coupled with observations that PCB causes comparable dose–response relationships for dendritic arborization and cognitive behavior in rodent models (Yang et al., 2009), provide strong support for a causal relationship between RyR-dependent effects of PCBs on dendritic growth and PCB-induced deficits in learning and memory.

Connectivity is influenced by not only the structural complexity of dendrites, but also by spine density (Chaudry & Vasudevan, 2022; Nanou & Catterall, 2018). In cultured primary rat hippocampal neurons and brain slices, PCB 95 significantly increased dendritic spine formation via RyR signaling and CREB-dependent upregulation of miR132 (Lesiak et al., 2014). The necessity of miR132 in this pathway is of particular interest since miR132 is also upregulated in the brain in response to valproic acid—a widely used model to induce autism phenotypes in mice (Hara et al., 2017). miR132 may be a convergent target for diverse environmental chemicals that confer autism risk. Interestingly, miR132 represses expression of MeCP2 (Klein et al., 2007), and dysfunction of MeCP2 is implicated in significant cognitive impairment, while, as mentioned earlier, both mutations and duplications of the *MECP2* gene are associated with Rett syndrome and autism (Cukier et al., 2012; LaSalle & Yasui, 2009; Percy, 2011). MiR132 has also been shown to interact with FMRP to regulate synapse formation (Edbauer et al., 2010).

Genetic mouse models engineered to express heritable human mutations that alter the fidelity of calcium signaling have been leveraged to test the hypothesis that genetic mutations converging on the same signaling pathways as PCBs increase susceptibility to the neurotoxic effects of PCBs. Mice that expressed a human gain-of-function mutation in the RyR, a CGG repeat expansion in the premutation range in the *Fmr1* gene, or both genetic mutations were exposed throughout gestation and lactation to varying doses of the MARBLES PCB mixture in the maternal diet. Morphometric and behavioral analyses of these mice revealed that dendritic morphogenesis and behavior were modulated by complex G×E interactions (Keil Stietz et al., 2021; Sethi et al., 2021). For example, in mouse cortical and hippocampal neurons, genotype influenced the dendritic response to PCBs in a dose, sex and brain region dependent manner. Expression of the RyR mutation or both the RyR and CGG expansion

mutations increased dendritic complexity at lower doses of PCBs compared to the dose required to elicit the same dendritic response in wildtype neurons (Keil Stietz et al., 2021). Behavioral studies indicated that developmental exposure of wildtype males to the MARBLES PCB mixture phenocopied social behavior phenotypes observed in mice expressing heritable human mutations in calcium signaling, while expression of these mutations alleviated PCB effects on ultrasonic vocalizations and repetitive behavior, and modified the dose-response relationships and sex-dependent effects of PCBs on social behavior (Sethi et al., 2021). Additional studies using these same mouse models and PCB exposures indicated that  $G \times E$  interactions influence the microbiome and intestinal physiology (Rude, Pusceddu, et al., 2019), as well as serum cytokine and chemokine levels (Matelski et al., 2020). Collectively, these observations support the hypothesis that heritable deficits in signaling pathways also impacted by environmental risk factors modify the neurotoxic response, which in turn influence autism risk.

#### 4.7 PBDEs as autism risk factors

Polybrominated diphenyl ethers (PBDEs) were produced for use as flame retardants in diverse consumer products, including furniture and children's clothing. These persistent organic pollutants (POPs) are of growing concern as putative autism risk factors because of widespread human exposure and their structural and toxicological similarity to NDL PCBs (Dingemans, Kock, & van den Berg, 2016; Pessah et al., 2019). Developmental exposure to BDE-47, one of the more prevalent of the 209 possible PBDE congeners detected in human tissues, impaired the performance of MeCP2 mutant mice in the Morris Water Maze task (Woods et al., 2012). *In vitro* studies revealed that PBDEs altered calcium signaling in primary rodent neurons via RyR-dependent mechanisms (Kim et al., 2011), modulated glutamate receptor signaling, disrupted TH signaling and increased production of reactive oxygen species via effects on mitochondrial function (Costa, Pellacani, Dao, Kavanagh, & Roque, 2015; Costa, Tagliaferri, Roque, & Pellacani, 2016; Dingemans et al., 2016). PBDEs have also been shown to alter hepatic biotransformation and *CYP* expression, an effect that varied depending on the enterotype (conventional *vs.* germ-free) of the exposed animal (Li et al., 2017).

Curiously, in contrast to NDL PCBs, neither BDE 47 nor BDE 49, two congeners detected in the human gestational environment, promoted

dendritic growth in primary rat hippocampal neurons (Chen, Lin, Dang, & Puschner, 2017). Rather both congeners delayed neuronal polarization resulting in significant inhibition of axonal outgrowth during the first few days *in vitro*. The axon inhibitory effects of these PBDE congeners occurred independent of cytotoxicity, and were blocked by pharmacological antagonism of RyR or siRNA knockdown of RyR2. These results demonstrate that the molecular and cellular mechanisms by which PBDEs interfere with neurodevelopment overlap are distinct from those of NDL PCBs. In addition, altered patterns of neuronal connectivity may contribute to the developmental neurotoxicity of PBDEs and increase autism risk in individuals with heritable autism risk factors that converge on calcium signaling and/or pathways that regulate neuronal connectivity (Table 2).

Epidemiological observations suggest that PBDE exposures are associated with reduced IQ and behavioral abnormalities (Pessah et al., 2019; Zhang et al., 2017). Associations between developmental PBDE exposures and abnormal executive function and attention control in young children, as well as impairments in externalizing behaviors (Vuong et al., 2018), have been reported. However, the literature regarding PBDE links to autism is conflicting. In one study of pregnant women, PBDE 28 levels were positively correlated with SRS (autistic behavior) scores in children aged 4–5, while levels of PBDE 85 were linked to fewer autistic behaviors (Braun et al., 2014). In another study of 100 children, PBDE levels were similar in children with autism *vs.* typically developing controls; however, there were no data regarding levels of PBDEs during prenatal development (Hertz-Picciotto et al., 2011). In a study of mother and child pairs in Northern California, maternal serum levels of PBDEs were lower in mothers with a child with autism; yet, sex may play a role in these associations as these effects were prominent in boys for whom there was an indication of increased autism risk, especially with PBDE 28 and PBDE 47, but not in girls (Lyll, Croen, Weiss, et al., 2017).



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## 5. Evolving areas of research

### 5.1 Emerging chemicals of concern

Increased awareness of the potential influence of environmental exposures on autism risk and/or severity has driven interest in determining which of the 80,000+ chemicals in the human chemosphere pose the greatest autism risk. This in turn has stimulated the development of experimental models for testing the impacts of environmental chemicals on phenotypes

of relevance to autism. Data from these studies combined with exposure monitoring data have identified several chemical classes of emerging concern, notably per- and polyfluoroalkyl substances (PFAS), including perfluorooctane sulfonate (PFOS).

In preclinical rodent models, lactational exposure to PFOS decreased learning and memory function and elevated glutamate and GABA levels in the hippocampus of adult mice (Mshaty et al., 2020). Developmental PFOS exposure also caused deficits in motor function, changed short-term and long-term plasticity in Purkinje cells, and altered levels of proteins involved in neurotransmission, including glutamate receptors (Ninomiya et al., 2022). Postnatal exposure to perfluorohexane sulfonate (PFHxS), perfluorooctanoic acid (PFOA) and PFOS altered adult behavior and cognitive function in mice, in part by modulating cholinergic signaling in the brain (Johansson, Fredriksson, & Eriksson, 2008; Viberg, Lee, & Eriksson, 2013). While PFOS are less well studied than PCBs and other legacy pollutants, there is increasing evidence that PFOS are worth investigating as putative autism risk factors.

Epidemiological data suggest that certain types of PFAS, such as PFOA, increase autism risk in a non-monotonic (U-shaped) dose-related manner, while mixtures of PFAS show an inverse dose relationship with autism (Skogheim et al., 2021). PFAS were found in serum of women in California with a child age 2–5, and longer breastfeeding was linked to lower serum levels in the mothers, indicating that lactation may be a source of PFAS in children (Kim, Bennett, Calafat, Hertz-Picciotto, & Shin, 2020). In a study of mother-child pairs in the CHARGE study (Childhood Autism Risk from Genetics and Environment), PFHxS and PFOS were higher in the serum of women who had a child with autism *vs.* typically developing controls (Shin, Bennett, Calafat, Tancredi, & Hertz-Picciotto, 2020). In 173 mother-child pairs from the MARBLES study, prenatal PFOA and perfluorononanoate (PFNA) levels were positively associated with autism risk, while PFHxS showed a negative association with autism risk (Oh, Bennett, Calafat, et al., 2021). In other studies, serum PFAS levels in children aged 5 and 7 were associated with behavioral problems at age 7 (Oulhote, Steuerwald, Debes, Weihe, & Grandjean, 2016). In 140 mother-child pairs from the MARBLES study, prenatal PFOA was inversely associated with scores for the Early Learning Composite, which is a measure of motor, visual and language function in children aged 2–3 (Oh, Schmidt, Tancredi, et al., 2021). However, two other studies that sampled maternal sera during early to mid-pregnancy found no or inverse associations between PFAS and autism diagnosis (Liew et al., 2015; Lyall et al., 2018).

The different outcomes observed between these studies likely result from differences in the study populations, including, location, year and stage of pregnancy at time of collection; differences in methodologies for measuring exposures; as well as well differences in clinical criteria used to diagnose autism. Despite the inconsistent findings, the available data suggest that PFAS warrant further investigation to better understand how much of a risk they pose to genetically susceptible individuals and to elucidate their mechanism(s) of developmental neurotoxicity to identify which genetic substrates are most susceptible.

## 5.2 Influence of environmental risk factors on autism co-morbidities

Children diagnosed with autism often suffer from several comorbid conditions, including GI complications as well as bladder dysfunction (von Gontard, Baeyens, Van Hoecke, Warzak, & Bachmann, 2011). The role of G×E interactions in inducing these comorbid conditions is currently understudied and discussed in a recent review (Panesar et al., 2020). As mentioned earlier, experimental evidence suggests that PCB exposures alter the gut microbiome (Li et al., 2017; Lim et al., 2020), which would be expected to alter GI function. PCBs may also contribute to GI dysfunction via mechanisms independent of effects on the gut microbiome. For example, developmental exposure to the MARBLES PCB mixture altered intestinal permeability and expression of inflammatory mediators in wild type mice, and these effects were exacerbated in mice with heritable mutations in calcium signaling (Li et al., 2017; Rude, Keogh, & Gareau, 2019). Interestingly, developmental exposure to the MARBLES PCB mixture influenced the ability of adult mice to urinate (Kennedy et al., 2022). Mechanistic studies of these observations are ongoing but suggest two testable possibilities: (i) PCBs directly affect peripheral target organs such as the intestine and bladder; and (ii) PCBs alter intestinal and bladder function indirectly via effects on the autonomic nervous system that innervates these organs. The latter hypothesis is derived from data linking disturbances in the autonomic nervous system to GI, bladder, and immune dysfunction (Matteoli & Boeckstaens, 2013; Muller et al., 2020; Roy & Green, 2019). The peripheral nervous system may be a convergence point through which environmental factors such as PCBs influence the manifestation of autism comorbidities. How the genetic substrate ties into these phenotypes is currently not understood, but the mechanisms detailed above for the central nervous system likely play a role in the peripheral nervous system.





## 6. Concluding remarks

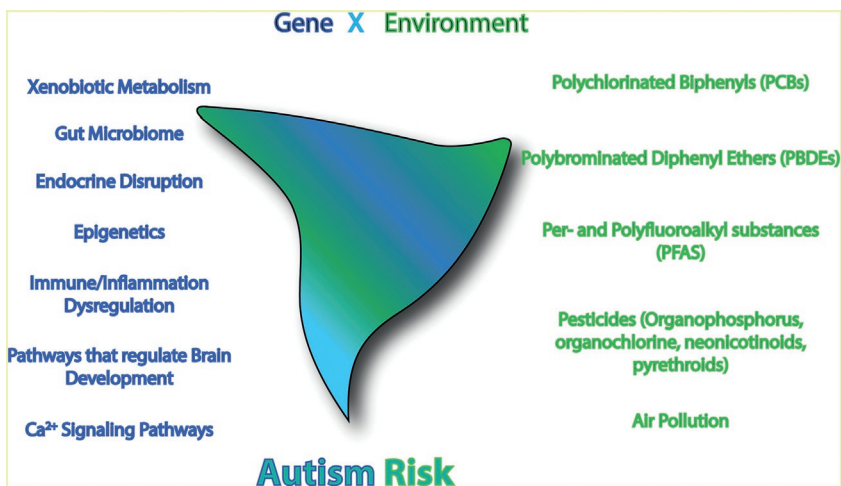
A significant contribution from environmental factors in determining autism risk and severity is consistent with both the rapid increase in autism rates and the clinical heterogeneity that is the hallmark of this neurodevelopmental condition. However, this phenotypic heterogeneity combined with the complex genetic substrate of autism significantly increases the challenge of identifying specific environmental factors that confer increased risk for autism as well as the genetic susceptibilities that are particularly vulnerable to these environmental factors. To close this significant data gap, we endorse the suggestion that research efforts focus on leveraging experimental models to identify mechanisms by which environmental factors interact with genetic factors to increase the risk of adverse neurodevelopmental outcomes of relevance to autism. Such mechanistic insights can then be used to develop rapid throughput screens for potential environmental risk factors, which in turn will inform and focus epidemiological studies.

The success of this strategy is predicated on choosing appropriate model systems. While a number of transgenic animals (mice, and more recently, rats) expressing autism-linked genetic mutations have been or are being developed, the costs associated with using these models for developmental neurotoxicity exposure studies limits their utility for early mechanistic and screening approaches (Lein et al., 2005). Such models do, however, serve an important role in confirming putative  $G \times E$  interactions identified in simpler systems. But for initial mechanistic and screening studies, we propose the use of *in vitro* models (such as primary neuronal cell cultures or human iPSC-derived neural systems) or simple systems-based models (such as *C. elegans* or *D. rerio*) that recapitulate the neurodevelopmental processes disrupted in autism. Ongoing research demonstrates that such models can be adapted for rapid throughput screening of multiple culture wells simultaneously using, for example, high content imaging systems to analyze dendritic morphology and synaptic density (Harrill, Robinette, & Mundy, 2011), microelectrode arrays to measure network activity as a measure of functional connectivity (Johnstone et al., 2010; Robinette, Harrill, Mundy, & Shafer, 2011), the FLIPR<sup>®</sup> to assess spontaneous calcium oscillations (Cao, Hammock, et al., 2012) and “omic” technologies to identify changes in molecular and biochemical targets (Modafferi et al., 2021). *In silico* approaches that leverage databases, such as the Comparative

Toxicogenomics Database, to interrogate chemical influences on the hundreds of autism susceptibility genes identified to date (Carter & Blizard, 2016) would also be an effective high-throughput approach for identifying potential autism-relevant G × E interactions.

Another consideration in studies of G × E interactions in autism is cross-talk between signaling systems and G × E mechanisms that influence neuronal connectivity, as well as between chemicals in mixtures (Fig. 1). For example, endocrine signaling regulates gene transcription of proinflammatory cytokines, and soluble mediators of the innate immune system, such as cytokines, can feed back on the brain to regulate endocrine signaling (Irwin & Cole, 2011). The immune system is also strongly influenced by the gut microbiome, and emerging evidence suggests that the microbiome influences not only peripheral immune calls, but also microglia in the brain (Lebovitz et al., 2018). There is also evidence that microbes within the human gut may play a significant role in the regulation of the brain via their influence on the production of inflammatory cytokines, antimicrobial peptides and neurotransmitters that affect the epigenome (Alam et al., 2017; Yousefi et al., 2022).

Clearly, work is urgently needed to better predict which combination of autism genes and environmental exposures pose the greatest autism risk. The fact that chemical exposures are more readily controlled than genetic



**Fig. 1** Autism risk is likely determined by cross talk between multiple signaling pathways, mechanisms of G × E interactions and interactions between structurally and mechanistically diverse chemicals in mixtures.

factors to prevent or mitigate the expression of autism-related traits coupled with the significant toll that autism places on autistic children, their families and society, provides a compelling reason to engage in this endeavor.

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