

# Sex-Specific Effects of Combined Exposure to Chemical and Non-chemical Stressors on Neuroendocrine Development: a Review of Recent Findings and Putative Mechanisms

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## Abstract

**Purpose of Review** Environmental toxicants and psychosocial stressors share many biological substrates and influence overlapping physiological pathways. Increasing evidence indicates stress-induced changes to the maternal milieu may prime rapidly developing physiological systems for disruption by concurrent or subsequent exposure to environmental chemicals. In this review, we highlight putative mechanisms underlying sex-specific susceptibility of the developing neuroendocrine system to the joint effects of stress or stress correlates and environmental toxicants (bisphenol A, alcohol, phthalates, lead, chlorpyrifos, and traffic-related air pollution). **Recent Findings** We provide evidence indicating that concurrent or tandem exposure to chemical and non-chemical stressors during windows of rapid development is associated with sex-specific synergistic, potentiated and reversed effects on several neuroendocrine endpoints related to hypothalamic-pituitary-adrenal axis function, sex steroid levels, neurotransmitter

circuits, and innate immune function. We additionally identify gaps, such as the role that the endocrine-active placenta plays, in our understanding of these complex interactions. Finally, we discuss future research needs, including the investigation of non-hormonal biomarkers of stress.

**Summary** We demonstrate multiple physiologic systems are impacted by joint exposure to chemical and non-chemical stressors differentially among males and females. Collectively, the results highlight the importance of evaluating sex-specific endpoints when investigating the neuroendocrine system and underscore the need to examine exposure to chemical toxicants within the context of the social environment.

**Keywords** Sexually dimorphic · Neurodevelopment · Stress · Chemical · Neurotoxicant · Prenatal

## Introduction

For decades, the fields of psychology and child development have embraced the concept that an “umbilical transference” [1] occurs during prenatal life, in which the developing fetus is not only susceptible to risks conferred by physical and chemical exposures, but is sensitive to the vicissitudes of maternal psychological state and affect. Indeed, in the 90 years since Freud inferred the importance of the maternal-fetal bond (“[there is] much more continuity between intra-uterine life and earliest infancy than the impressive caesura of birth would have us believe” [2]), maternal emotional state and hormonal fluctuations have been associated with spontaneous abortion, fetal distress, premature labor, and other pregnancy complications [3–5].

More recently, the fields of toxicology and environmental epidemiology have begun to adopt these principles and move towards an “exposome” approach, in which an individual’s

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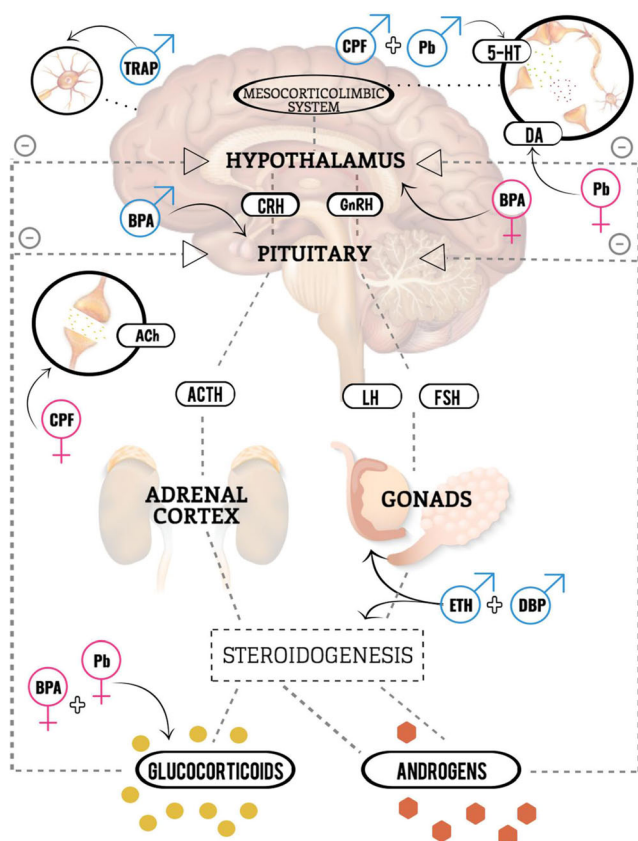
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cumulative “internal chemical environment” is thought to reflect exposure from both exogenous sources (i.e., environmental toxicants) and endogenous processes (i.e., stress-induced hormonal changes) [6].

From a health perspective, embracing the exposome is critical as environmental toxicants and psychosocial stressors share many biological substrates and increasing evidence indicates that stress-induced changes to the maternal milieu may prime rapidly developing physiological systems for disruption by concurrent or subsequent exposure to environmental chemicals and vice versa [7, 8].

In this review, we summarize four putative mechanisms underlying sex-specific susceptibility of the developing neuroendocrine system to the joint effects of psychosocial stress and environmental toxicants (Fig. 1). We focus on this system given the sex bias of many neurocognitive and behavioral disorders [9] and evidence demonstrating stress and an array of toxicants independently disrupt neurodevelopmental trajectories and alter programming of the fetal brain, including organization of sexually dimorphic regions [10, 11, 12]. We



**Fig. 1** Conceptual model illustrating sex-specific neuroendocrine targets of chemical and non-chemical stressors. All toxicant associations reflect interactions with stress; however, stress is not visually depicted. 5-HT serotonin, ACh acetylcholine, ACTH adrenocorticotropic hormone, BPA bisphenol A, CRH corticotropin releasing hormone, CPF chlorpyrifos, DA dopamine, DBP dibutyl phthalate, ETH alcohol, FSH follicular stimulating hormone, GnRH gonadotropin releasing hormone, LH luteinizing hormone, Pb lead, TRAP traffic-related air pollution

support each mechanism with examples from animal research, and when available, we discuss parallel epidemiologic findings. We draw from studies examining six well-established developmental neurotoxicants, including bisphenol A (BPA), alcohol, phthalates, lead, chlorpyrifos, and traffic-related air pollution. An exhaustive review of sex-specific neurodevelopmental effects associated with isolated exposure to psychosocial stress and these toxicants is beyond the scope of this paper; however, when available, we point readers to previously published review articles. Finally, we identify gaps in our current understanding of these complex interactions and discuss future research needs.

## Background

### Measures of Stress

Stress is a complex, multilevel construct characterized by cognitive appraisal of potentially stressful stimuli and consequent physiological reactions at both the cellular and emotional levels. Variation in stress responses reflects features of the stimuli (i.e., context, intensity, chronicity) and individual (i.e., sex, life stage, appraisal, coping capacity), thus requiring a diverse set of instruments and protocols for measurement. In epidemiologic research, measures of physical strain (e.g., malnutrition, sleep deprivation) and socioeconomic correlates of stress (e.g., education, resource accessibility), as well as scales of negative life events, stress perception, and negative affect are often used [13]. In experimental animal studies, common protocols include physical restraint, forced swimming or restricted access to bedding material. Additionally, both animal and human studies frequently measure biomarkers of stress, such as glucocorticoids (i.e., cortisol in humans or corticosterone in rodents), under basal conditions and/or following exposure to stressful stimuli. Similarly, researchers can evaluate the timing and intensity of stress responses by examining physiologic and molecular changes following administration of synthetic glucocorticoids.

### Mechanism 1: Disrupted Hypothalamic-Pituitary-Adrenal Axis Function

Circulating glucocorticoid levels are maintained by the hypothalamic-pituitary-adrenal (HPA) axis, which regulates physiological responses to potentially stressful stimuli [14]. The HPA axis includes the hypothalamus and pituitary gland located in the brain, and the adrenal glands, which are situated above the kidneys. In response to signals from brain nuclei involved in emotion-regulation, hypothalamic neuroendocrine cells produce corticotropin releasing hormone (CRH), which triggers secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH signals the adrenal

cortex to synthesize and release cholesterol, which undergoes steroidogenic conversion to glucocorticoids, mineralocorticoids, and to a lesser extent androgens (i.e., testosterone). Glucocorticoid receptors located on the hypothalamus and pituitary detect circulating levels and terminate axis activity through a feedback inhibition mechanism.

## Bisphenol A

BPA is an endocrine disrupting chemical associated with sex-specific neurobehavioral problems in children [15]. It has been widely used in food cans, plastic bottles, and other consumer products leading to nearly ubiquitous human exposure [15]. In silica research indicates BPA is a glucocorticoid receptor agonist [16], and it has been associated with altered HPA axis function in juvenile trout [17] and pregnant women [18]. During pregnancy, surges in glucocorticoid levels are essential for normal maturation of several organ systems; however, elevated glucocorticoids at incorrect developmental stages have been shown to disrupt fetal programming of the HPA axis [19, 20].

Based on these factors, Pantagiotidou et al. investigated sex-specific effects of perinatal exposure to BPA on HPA axis responsiveness during adolescence using a murine model [21]. Among female rats, BPA was associated with altered basal corticosterone (increased) and hypothalamic glucocorticoid receptor (decreased) levels. In response to acute stress (forced swimming), BPA-exposed females exhibited anxious coping behaviors and a dampened corticosterone response with failed downregulation of hypothalamic glucocorticoid receptor expression. In contrast, BPA-exposed males did not

show altered basal HPA axis function; however, they failed to upregulate pituitary CRH receptor 1 expression in response to acute stress (Table 1). Taken together, these findings suggest prenatal BPA exposure may program a hyperactive HPA axis with impaired negative feedback responsiveness to circulating corticosterone levels among females and a dampened stress response among males. Notably, HPA axis hyperactivity has been associated with anxiety and depression-like behaviors in rats [33] and diagnosis of anxiety and major depressive disorder in children and adolescents [34]. These findings suggest sex-specific reprogramming of the HPA axis by in utero exposure to BPA may permanently alter individual responses to stressful stimuli and contribute to life-long neuropsychological problems.

## Mechanism 2: Altered Sex Steroid Levels

Similar to adrenal steroidogenesis, the gonads produce sex steroids under the control of the hypothalamic-pituitary-gonadal (HPG) axis. Precisely timed surges of gonadal and adrenal sex steroids are critical for sexually dimorphic differentiation, including de-feminization and masculinization of the male brain [9, 35, 36].

## Alcohol

Increasing evidence indicates stressful stimuli [37] and environmental toxicants [38] disrupt the fetal HPG axis. Given these findings, Ward et al. conducted a series of rodent studies to examine the effects of combined exposure to prenatal stress

**Table 1** Summary of effects from combined exposure to stress and several developmental toxicants on neuroendocrine and immune endpoints in rodents

Toxicant	Stressor	Male	Female	Ref
BPA (prenatal)	Forced swimming (adolescence)	Failed upregulation of pituitary corticotropin releasing hormone receptor 1	↑ Anxious coping behavior, ↓ corticosterone response; failed downregulation of hypothalamic glucocorticoid receptor expression	[21]
Alcohol (prenatal)	Restraint (prenatal)	Delayed and abbreviated fetal testosterone surge, feminized sexual behavior	Not studied	[22, 23]
DBP (prenatal)	Dexamethasone (prenatal)	↓ Fetal intra-testicular testosterone levels, ↓ expression of gonadal steroidogenesis genes, ↑ severity and incidence of reproductive organ malformations	Not studied	[24]
Pb (prenatal)	Restraint (prenatal)	Disrupted mesocorticolimbic serotonin function and altered delay discounting behavioral performance (trend only, not significant)	↓ Frontal cortex dopamine levels; ↑ circulating corticosterone levels, ↑ learning deficits; ↑ impulsive choice behavior	[25–28]
Chlorpyrifos (neonatal)	Dexamethasone (prenatal)	↓ Serotonin turnover, ↓ upregulation of serotonin receptor and transport protein expression, ↑ hyperactivity	↓ Choline transport protein binding, ↓ choline acetyltransferase activity, ↓ postsynaptic receptor binding	[29–31]
DEP (prenatal)	Nest restriction (prenatal)	↑ Expression of microglial toll-like receptor-4 and caspase-1, ↑ pro-inflammatory bias, ↑ anxiety	No interaction observed	[32]

BPA bisphenol A, DBP dibutyl phthalate, Pb lead, DEP diesel exhaust particles

(restraint) and alcohol on fetal testosterone patterns and later sexual behavior [22]. Male rats born to dams exposed to alcohol or stress during pregnancy were characterized by a testosterone surge (timing and duration) similar to that of controls; however, at each gestational day, levels of testosterone were elevated in the alcohol-only group and depressed in the stress-only group [22]. Among males in the combined exposure group, the fetal testosterone surge was significantly delayed and abbreviated ( $p = 0.02$ ) compared to the unexposed and single-exposed groups [22]. As adults, males in the combined exposure group displayed feminized sexual behavior (e.g., lordosis) and reduced incidence of copulation with estrous females (Table 1) [23, 39]. Notably, in typically developing rats, the fetal testosterone surge corresponds with development of the sexually dimorphic nucleus in the hypothalamic preoptic area (SDN-POA), which plays important roles in controlling expression of sexual behaviors [37]. These findings suggest that combined exposure to alcohol and stress may desynchronize the temporal overlap between the fetal testosterone surge and development of the SDN-POA, resulting in feminization of the male brain.

### Phthalates

Consistent with the effects of alcohol, exposure to phthalates during the fetal masculinization window has been shown to alter rat gonadal steroidogenesis [40–42] and disrupt development of the male reproductive tract. In humans, prenatal exposure to phthalates has been associated with altered sex steroid levels [43–45] and de-masculinized phenotypes among boys, including reduced anogenital distance [46]. In turn, anogenital distance is considered a sensitive marker of androgen activity in early gestation [47] and correlates with sex-specific neurobehaviors [48]. Dibutyl phthalate (DBP) is a plasticizer that has been used extensively in toys and personal care products [49]. Given nearly ubiquitous human exposure to both DBP and stressful stimuli, Drake et al. used a rat model to investigate the effects of concurrent exposure to DBP and the synthetic glucocorticoid dexamethasone [24]. Compared to unexposed controls, male offspring prenatally exposed to DBP had lower fetal intra-testicular testosterone levels, reduced expression of key genes (*Star*, *CYP11a1*) involved in gonadal steroidogenesis, and several anatomical malformations, including shortened anogenital distance. Exposure to dexamethasone alone showed no effects on male reproductive endpoints, however, when combined with DBP it enhanced the severity or incidence of most DBP-induced effects. Furthermore, combined exposure revealed effects on anogenital distance at lower doses of DBP (Table 1).

Diethylhexyl phthalate (DEHP) is a second anti-androgenic phthalate that is used to enhance flexibility of plastic-based consumer products [50]. Using data from a multi-center birth cohort, Barrett et al. investigated prenatal

exposure to stress and DEHP among a sample of infants ( $n = 137$  boys,  $n = 136$  girls) [51]. Stress was measured using a scale of stressful life events administered to couples during pregnancy and DEHP metabolites were measured in a maternal spot urine sample. Consistent with previous findings [52], stressful life events and DEHP exposure were independently associated with reduced anogenital distance among boys, albeit the association with stressful life events was not statistically significant [51]. Interestingly, when stratified by stress ( $< 4$  vs.  $4+$  stressful life events), DEHP metabolites were associated with reduced anogenital distance only among boys in the low stress group. These findings suggest that among males, stress in combination with DEHP exposure may interact such that their joint exposure protects against the anti-androgenic effects conferred by each in isolation. Among girls, prenatal stress was associated with significantly longer anogenital distance, indicative of a masculinizing phenotype; however, no interaction with DEHP metabolites was observed. Importantly, given the relatively small size of the study sample, it is important that these findings be replicated by future studies.

Collectively, these findings provide evidence that in rats, exposure to stress during pregnancy may augment the effects of concurrent exposure to environmental chemicals on male reproductive track outcomes and development of sexually dimorphic brain regions; however, more research is needed to translate these findings to humans.

### Mechanism 3: Changes to Neurotransmitter Systems

The brain is organized into complex neural networks that rely on the action of neurotransmitter-specific synapses for communication. Several of these circuits, such as the mesocorticolimbic dopamine circuit, also innervate key regulatory systems, including the HPA axis [53]. The mesocorticolimbic neurotransmitter system projects from the ventral tegmental area to the nucleus accumbens, striatum, cortex, and limbic centers; its coordinated function is important in motivation, memory, and positive reinforcement of emotion-related behaviors [54].

### Lead

Prenatal exposure to Pb and stress have each been shown to independently act on the mesocorticolimbic circuit [25, 55], leading Cory-Slechta et al. to investigate the effects of combined exposure in a series of rat studies. The researchers found that among adult female rats prenatally exposed to acute stress (restraint) and Pb, but not either in isolation, frontal cortex dopamine levels were reduced and circulating corticosterone levels were elevated [26]. Females in the combined exposure group also exhibited learning deficits [27] and increased rates

of stress-induced food reward responding, an indicator of impulsive choice behavior [25]. Parallel findings were not observed among males. In a subsequent study, the research group found indications of a trend towards disrupted mesocorticolimbic serotonin function and altered delay discounting behavioral performance among males exposed to Pb and stress; however, a statistically significant interaction was not observed [28]. Serotonin is a critical mediator of dopamine function [56], is important to HPA axis programming [57], and has been associated with sex-specific impulsive choice behavior in rats [58] and humans [59]. While substantial evidence indicates that stress and Pb act at the intersection of the mesocorticolimbic dopamine circuit and HPA axis, future research is needed to understand whether serotonin modulates this interaction.

### Chlorpyrifos

Chlorpyrifos is a widely used agricultural pesticide [60] that disrupts neurotransmitter circuits by inhibiting acetylcholinesterase, the enzyme responsible for breaking down acetylcholine at neuromuscular junctions. Unsurprisingly, human exposure results in similar effects on acetylcholine systems [61], as well as disruption of serotonin circuits [62, 63]. Among children, prenatal exposure has been associated with tremor [64] and lower scores on measures of cognitive and neurobehavioral development [65, 66]. Glucocorticoids also target cholinergic [67] and serotonergic [68] circuits and recent findings suggest prenatal exposure to glucocorticoids may prime these neurotransmitter systems for enhanced disruption by subsequent chlorpyrifos exposure. Using a murine model, Slotkin et al. examined several neurochemical and behavioral endpoints in offspring exposed to the synthetic glucocorticoid dexamethasone and/or chlorpyrifos during the prenatal and neonatal periods, respectively [29–31]. Among males, each exposure was associated with reduced presynaptic acetylcholine activity and combined exposure demonstrated additive effects on this endpoint. Conversely, among females, dexamethasone and chlorpyrifos were each associated with increased presynaptic activity, whereas tandem exposure was associated with significantly reduced presynaptic activity (indexed by decreased choline transport protein binding and reduced choline acetyltransferase activity) and lost postsynaptic reactivity (indexed by decreased postsynaptic receptor binding) [30]. Tandem exposure was also associated with enhanced deficiencies in serotonin turnover, an indicator of presynaptic impulse activity, and attenuated upregulation of both serotonin receptor and transport protein expression [29]. Notably, serotonin effects were stronger among male pups, who additionally exhibited significantly greater hyperactivity compared to males in the control and single-exposure groups (Table 1) [31]. These findings suggest prenatal exposure to elevated glucocorticoids may enhance vulnerability of

cholinergic (girls) and serotonergic (boys) systems to disruption by postnatal chlorpyrifos exposure.

### Mechanism 4: Immune Dysregulation

Exposure to stress during fetal and neonatal life has been shown to alter fetal immune pathways [69–71], which play important roles in development of sexually dimorphic brain regions. For example, research conducted in male rodents suggests that increased estradiol levels resulting from aromatization of testosterone upregulates several microglial immune response genes resulting in the release of inflammatory signaling molecules (e.g., cytokines, prostaglandins) [72]. In turn, elevated prostaglandins trigger a signaling cascade that ultimately augments medial preoptic area dendritic spine density, which plays a central role in the ability of males to detect olfactory cues from sexually receptive females [72]. This complex molecular pathway has been substantiated by experimental studies demonstrating male copulatory behavior during adulthood is completely suppressed among rats subjected to microglial ablation during the neonatal period [73]. Additional pathways through which the immune system influences programming of the developing brain have been reviewed by Bilbo et al. [74].

### Traffic-Related Air Pollution

Prenatal exposure to traffic-related air pollution is associated with sex-specific disruption of brain development, neurocognitive and behavioral endpoints, and innate immune function [75]. The effects of combined exposure to stress and diesel exhaust particles on immune markers was recently studied using a murine model. Bolton et al. found that male rat pups born to dams exposed to diesel exhaust and subjected to nest restriction during pregnancy had significantly elevated expression of microglial toll-like receptor-4 (TLR4) and its downstream effector caspase-1. TLR4 is an innate immune receptor responsive to both exogenous and endogenous danger-associated molecular patterns [32]. As adults, male pups in the combined exposure group also exhibited a greater pro-inflammatory bias (pro-inflammatory IL-1 $\beta$ /anti-inflammatory IL-10 ratio) in microglial-derived cytokine levels compared to females. Subsequent analyses demonstrated these sex-specific molecular changes extended to cognitive and behavioral impairments, with males displaying significant hippocampal-dependent memory deficiency and increased anxiety-like behavior compared to males in the control and single-exposure groups (Table 1) [32]. These findings suggest maternal stress-induced changes in TLR4 signaling may enhance the effects of diesel exhaust exposure through microglia-mediated inflammation pathways within the fetal rat brain.

Using data from a Boston, MA-based birth cohort, we previously investigated relationships between maternal report of negative life events during pregnancy and prenatal exposure to black carbon, a measure of traffic-related air pollution, on memory and learning domains among 6-year-old children ( $n = 145$  boys,  $n = 113$  girls) [76]. Consistent with Bolton et al., we found that high exposure to black carbon was associated with significant deficits in attention-concentration scores only among boys born to mothers with high negative life event scores. While we did not study immune pathways, previous research in children has demonstrated stress [77] and black carbon [78] are associated with significant increases in pro-inflammatory IL-1 $\beta$  levels, supporting the role of the immune system as a potential mediator of our observed findings.

### Summary of Mechanisms

Collectively, the studies reviewed demonstrate that psychosocial stress and chemical toxicants interact to disrupt several physiological systems important to neurodevelopment and that these interactions vary by sex. However, given the limited research on these complex interactions, especially among humans, consistent patterns of disruption across chemicals, stressors, and physiological systems remain poorly understood.

### Future Research Needs

#### Role of the Placenta

While the studies summarized here focus directly on the fetal and maternal systems, emerging research indicates the placenta also plays a critical role in shaping sex-specific neurodevelopment [79]. Despite its design as a constitutional barrier between the mother and fetus, the placenta is penetrated by several neurodevelopmental toxicants and recent research indicates it is sensitive to changes in maternal state [79–81]. For example, in a mouse model, exposure to stressful stimuli during pregnancy downregulates placental expression of O-linked-N-glycosyl transferase (*OGT*), an x-linked gene involved in regulating epigenetic modification of a global repressive histone mark (H3K27me3) [82•, 83]. Notably, *OGT* escapes x-inactivation, leading to basal levels that are twice as low in males compared to females [82•, 83]. The additional stress-induced decrease in *OGT* may result in an activated state among males via reduced transcriptional repression, ultimately rendering males more sensitive to concurrent or subsequent insults. Moreover, prenatal exposure to stress has been shown to significantly reduce associations between *OGT* and the 17-beta-hydroxysteroid dehydrogenase-3 (*HSD17 $\beta$ 3*) gene locus in male placentas. This decrease

results in a corresponding reduction in placental expression of *HSD17 $\beta$ 3*, which is responsible for converting androstenedione to testosterone [82•]. As expected, prenatally stressed male mice present with increased androstenedione and decreased testosterone, as well as a dysmasculinized behavioral phenotype characterized by stress responses, cognitive function, and spatial strategies more similar to control females than control males. Despite these findings, no studies have investigated the sex-specific combined effects of stress and neurotoxicants on placental structure or function in humans. Future research at the intersection of the maternal-placental-fetal unit is needed to more fully understand how gestational perturbations affect placental function, including altered gene expression patterns.

### Improved Biomarkers of Stress

The majority of biomarkers currently used as indicators of stress are hormones (i.e., cortisol), which typically fluctuate in response to acute stress [84], may not accurately reflect maternal stress responses during pregnancy due to altered endocrine system homeostasis [85] and are affected by variation in several enzymes, including placental *HSD11 $\beta$ 2*, which converts cortisol to inactive cortisone [86]. Recently, telomeres have been identified as a potential biomarker of cumulative wear and tear on the body [87, 88•]. Telomeres are repetitive, non-coding T<sub>2</sub>AG<sub>3</sub> sequences located at terminal chromosome ends. During cell division, chromosomes erode owing to limitations of DNA replication machinery, thus telomeres serve a self-sacrificing role against damage and degradation of protein coding regions [89]. Several recent epidemiological studies have demonstrated associations between early-life social disadvantage and shorter telomere length [90–93]; however, these studies are largely limited by cross-sectional designs, small sample sizes, and retrospective reporting of childhood experiences. Future research investigating telomere dynamics during pregnancy and throughout early life is needed to understand whether telomeres can serve as a stress-sensitive biomarker during periods of rapid growth and development.

### Expanded Research in Humans

As is evident from our focus on animal research, human studies investigating sex-specific neuroendocrine effects of developmental exposure to chemical and non-chemical stressors is limited. While animal research provides a unique opportunity to experimentally manipulate and control study conditions, substantial anatomical, functional, developmental, and behavioral differences between species limit the generalizability of results to humans. For example, rat adrenal glands do not produce androgens, which are important contributors to sexually dimorphic differentiation of the brain in humans [94]. Likewise, the masculinization programming window is only

3–5 days in rats compared to 4–6 weeks in humans, potentially providing a greater time-opportunity for physiological disruption or recovery [24]. More observational epidemiology research investigating stress-chemical-sex interactions is needed to confirm the biological mechanisms elucidated by animal research.

### Investigation of Other Systems and Mechanisms

The reviewed studies do not encompass all psychosocial stressors, toxicants, physiological systems, or biological mechanisms known to influence brain development, but rather were selected to highlight enhanced disruption of pathways central to sex-specific programming. Moreover, while reviewed separately, these pathways overlap extensively and should be conceptualized as contributing to a single integrated system. For example, the immune system plays an important role in regulating levels of stress-sensitive neurotransmitters [95]; in turn, neurotransmitters influence sex steroid levels via modulation of the HPG axis at the level of the hypothalamus [96]. Moreover, the extent to which stress may act to increase exposure at the biological level is poorly understood. For example, rats exposed to stress have increased brain Pb [28] and decreased blood alcohol [97] levels compared to non-stressed animals exposed to the same dose of chemical. These results suggest that rather than directly acting on overlapping biological substrates, stress may alter blood brain barrier permeability, alcohol metabolism, and/or other pathways involved in toxicant distribution and excretion. Expanded research on the integration of these systems, as well as studies on other biological systems (i.e., autonomic) and cellular mechanisms (i.e., oxidative stress) sensitive to stress and chemical toxicants is needed to more fully understand the pathways through which these exposures interact.

### Implications for Health Disparities

Members of low-income, minority communities experience more frequent negative life events, such as witnessing violence and suffering discrimination, which in turn may activate stress responses and precipitate feelings of anxiety, exclusion, and anger [98–102]. Likewise, the multiple challenges associated with financial strain, such as inadequate housing conditions, inability to afford food, and reduced access to health care, can tax individual coping strategies and lead to heightened emotional distress [103, 104]. In addition, parents facing multiple adversities are less likely to spend time at home (i.e., due to working multiple jobs with longer commutes and unfavorable shifts [105]) and are more likely to employ controlling, restrictive, and punitive parenting strategies, often as an adaptive and protective response to neighborhood crime or other dangerous circumstances [104].

As described extensively by the environmental justice literature, minority and socioeconomically disadvantaged individuals not only experience greater levels of psychosocial stress, but often bear a disproportionate burden of environmental risk [106, 107, 108]. For example, nationwide statistics indicate members of racial and ethnic minorities are more likely to live within 150 meters of a major US highway, putting these groups at increased risk for exposure to traffic-related air pollution [109]. Likewise, exposure to Pb has historically been higher among black [110] and low-income [111] children, who disproportionately live in urban neighborhoods with older housing that may contain deteriorating lead-based paint.

The socioeconomic and environmental challenges faced by these populations likely contribute to the persistence of health disparities across ethnic and economic groups in the USA [109]. For example, the rate of premature birth is significantly higher among black (17%) compared to white (11%) infants [109]. Premature birth is estimated to account for one third of all infant deaths and is associated with numerous childhood and later life disorders, including neurocognitive and behavioral problems [112]. Notably, black children (8.4%) and those living below the federal poverty level (11%) are more likely to be diagnosed with a learning disability or attention deficit hyperactivity disorder compared to white children (7.5%) and those living at or above 200% of the poverty level (5.8%), respectively [113]. Likewise, infants born to mothers with less than a high school education, an indicator of socioeconomic status, are nearly twice as likely to die in the first year of life and approximately six times more likely to be rated in poor or fair health during childhood [114]. Similar trends have been documented for other indicators of socioeconomic status (i.e., family structure) and childhood morbidities (i.e., asthma) [113].

### Conclusions

Health inequalities, including disparities in neurocognitive and behavioral outcomes, persist across ethnic and economic groups in the USA. As demonstrated here, multiple sexually dimorphic biological systems involved in programming the developing brain are susceptible to enhanced disruption by concurrent or consecutive exposure to psychosocial stress and chemical toxicants, which often co-occur among minority and socioeconomically disadvantaged communities. The reviewed studies highlight the importance of examining exposure to chemical toxicants within the context of the social environment, as well as the need to consider the influence of sex when investigating neuroendocrine and immune endpoints. Despite challenges associated with investigating these relationships among humans, such as the large sample size requirements needed to investigate three-way interactions in

observational studies and ethical considerations associated with randomized controlled trials, future research focused on studying these interactions among human populations is critically needed.

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#### Compliance with Ethical Standards

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**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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