

Environmental Health Factors and Sexually Dimorphic Differences in Behavioral Disruptions

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Abstract Mounting evidence suggests that environmental factors—in particular, those that we are exposed to during perinatal life—can dramatically shape the organism’s risk for later diseases, including neurobehavioral disorders. However, depending on the environmental insult, one sex may demonstrate greater vulnerability than the other sex. Herein, we focus on two well-defined extrinsic environmental factors that lead to sexually dimorphic behavioral differences in animal models and linkage in human epidemiological studies. These include maternal or psychosocial stress (such as social stress) and exposure to endocrine-disrupting compounds (such as one of the most prevalent, bisphenol A [BPA]). In general, the evidence suggests that early environmental exposures, such as BPA and stress, lead to more pronounced behavioral deficits in males than in females, whereas female neurobehavioral patterns are more vulnerable to later in life stress. These findings highlight the importance of considering sex

differences and developmental timing when examining the effects of environmental factors on later neurobehavioral outcomes.

Keywords Developmental Origins of Health and Disease · *In Utero* Environment · Stress · Endocrine Disruptors · Bisphenol A · Cognition · Anxiety · Sexual Selection · Social and Reproductive Behaviors · Glucocorticoids · Anhedonia · Sex Differences · Gonadal Hormones

Introduction

The notion that many adult diseases originate from early environmental changes has gained currency in the past decade [1–3, 4•]. Several systems—in particular, the reproductive and central nervous systems—are programmed by developmental exposure to steroid hormones [5–12] and genes carried on the Y chromosome [13•]. Sexually dimorphic responses to environmental changes might originate from variable placental responses to environmental exposures, which may buffer the fetus of one sex more than the other [14–16]. For the purpose of this review, a sexually dimorphic response will be considered a phenotypic effect that either differs in absolute occurrence between the sexes (with a response present in one sex but absent in the other) or a significant difference in the magnitude of the intensity. For instance, early reports indicated that certain toxicants and food additives lead to kidney tumors in male but not female rats or mice [17, 18]. From these original reports, extrinsic factors have been reported to lead to varying degrees of sexually dimorphic responses—including, most recently, in neurobehavioral endpoints, which will be the primary focus of this review. With the National Institutes of Health (NIH) requesting a stronger emphasis on reporting health outcomes in both sexes, it is likely that research in the coming decades will further elucidate how

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various environmental cues result in dramatic sexually dimorphic differences.

Sexually selected cognitive traits might be especially vulnerable to extrinsic environmental changes [19]. As originally defined by Darwin [20], such traits promote intrasexual competition and intersexual choice of mating partners [20, 21]. Female mating preferences can drive the evolution of anatomical or behavioral traits in males and, in some cases, male mating preferences have been found to exert selection on female traits [22]. Expression of sexually selected behaviors in mature animals is programmed by developmental (fetal and neonatal or perinatal) exposure of the brain to steroid hormones (an organizational effect) and is maintained later in life by these same hormones—in particular, testosterone (an activational effect) [19, 23].

Environmental factors may abolish or augment the normal sex-specific brain programming or organizational effects necessary for sexually selected and other sexually dimorphic behaviors, leading to later behavioral deficits [1, 19, 24•, 25]. These changes could have a long-lasting impact on how endogenous hormones act in mature individuals.

The cerebral cortex, hippocampus, and hypothalamus (including the arcuate, ventromedial, and paraventricular nuclei) are key brain regions that demonstrate pronounced sexually dimorphic differences in neural programming [26]. While androgen receptors (ARs) are expressed in these regions, many testosterone-mediated neurobehavioral effects are due to aromatization of testosterone to estrogen [27–30]. Hippocampal development is dependent upon this steroid conversion [27, 28]. Being lipophilic, these circulating steroid hormones, along with many endocrine-disrupting compounds (EDCs), can easily cross the blood–brain barrier. Endogenous and exogenous steroids bind to their cognate receptors, including ARs, estrogen receptor (ESR)1, and ESR2, which are widely expressed in these brain regions [31–37]. There are also sex differences in the expression of these steroid hormone receptors in the brain. For example, in the medial preoptic area (mPOA) of males, the *Esr1* promoter is hypermethylated and *Esr1* expression is reduced, relative to that in females [38]. In contrast, neonatal female pups treated with estradiol exhibit a masculinized DNA methylation pattern for *Esr1*. It is also clear that EDCs, such as bisphenol A (BPA), can alter, in a sex-dependent manner, the neural expression of *Esr1* and *Esr2* [33, 39, 40], which may be one mechanism by which these extrinsic factors can either ablate or heighten sex-specific behavioral responses.

While various environmental factors have been linked to sex-specific disruptions, this review will focus on two well-characterized factors: perinatal exposure to EDCs, with the prototype being BPA, and psychosocial stress. We will consider how such environmental factors affect sexually selected behavioral traits in adults, including cognition and reproductive and emotional behaviors.

Sexually Dimorphic Behavioral Differences Associated with Endocrine-Disrupting Compounds

Bisphenol A (BPA)

Most EDCs are manufactured chemicals [41], and, of these, BPA is one of the most mass produced, with production exceeding 8 billion pounds per year [42, 43]. One known action of BPA is binding and activation of ESRs [43], leading to disrupted development of hormone-dependent systems. The pervasiveness of this chemical predicts widespread and continued exposure of animals and humans [42, 43]. BPA is almost ubiquitously found in people; it is detectable in the urine of 93 % of the US population [44], as well as in fetal plasma, placental tissue [45], and breast milk [46]. Results from animal models and human studies indicate that exposure to BPA induces sex-specific effects in three general categories: (1) cognitive function, (2) emotional function (e.g., anxiety), and (3) sociosexual behaviors (Table 1).

Sexually mature, polygamous male deer mice (*Peromyscus maniculatus bairdii*) exhibit enhanced spatial navigational learning and memory, allowing them to locate potential female partners, which are widely dispersed throughout the environment [47]. Consequently, this behavior might be considered a sexually selected cognitive trait, which requires prenatal exposure to testosterone and photoperiod-dependent increases in this same hormone [47, 48]. Developmental exposure to environmentally relevant concentrations of BPA or ethinyl estradiol (EE) through the maternal diet compromises this behavior in males, as determined when both sexes are tested at adulthood in a dry-land spatial navigation maze (a Barnes maze) [24•, 49]. Under the notion that BPA may act through its weak binding of ESR1/ESR2 [43], the US Food and Drug Administration (FDA) has mandated that any study that is to be considered in influencing policy decisions must include EE as a positive control.

Male imprinting control region (ICR) mice exposed to BPA as adults also exhibit impaired spatial and passive avoidance memory, as evidenced by their performance in the Morris water maze and footshock testing, whereas these deficiencies are not observed in exposed females [50]. These differences may be mediated by early exposure to estrogens or testosterone, which affects development of the hippocampus and cerebral cortex [48, 51–53].

In control, non-treated female deer mice, spatial navigational ability is not enhanced when they become sexually mature, as increased exploration and expansion of the home range may be disadvantageous, with an increased predation risk. However, females that are developmentally exposed to a low dose of BPA or EE at doses comparable to human exposure exhibit masculinized or increased spatial abilities and exploratory behaviors [24•, 49].

Table 1 Example animal model and human epidemiological studies linking bisphenol A (BPA) exposure and sex-specific behavioral alterations

Publication(s)	Animal model/ human cohort population	EDC(s) tested or correlation analysis performed	Dosing regimen / method to measure BPA concentrations	Major findings
Jasarevic et al., 2011; Jasarevic et al. 2013 [24, 49]	Deer mice (<i>Peromyscus maniculatus bairdii</i>)	BPA and Ethinyl estradiol (EE)	50 µg BPA/kg feed weight (FW), 5 mg BPA/kg FW, 50 mg BPA/kg FW, and 0.1 ppb EE administered two weeks prior to conception through lactation in the maternal diet. Both sexes were exposed and examined.	<ul style="list-style-type: none"> Developmental exposure of males through the maternal to two doses (5 mg/kg feed weight and 50 mg/kg feed weight) or EE (0.1 ppb) led to cognitive deficits, as evidenced by prolonged latency and increased error rate compared to control males in the Barnes dry land spatial navigational maze and inability to convert to the direct search strategy. BPA- and EE-exposed males were also more anxious, as evidenced by increased time in the closed arms and less time spent in the open arms of the Elevated Plus Maze (EPM) relative to control males. In contrast, 5 mg BPA/kg feed weight and EE exposure led to masculinized spatial navigational ability in exposed females relative to control females. No effect on anxiety behaviors was observed in BPA- or EE-exposed females. In mate choice experiments, control and BPA-exposed females preferred control over BPA-exposed males.
Cox et al., 2010 [58]	C57B16 mice	BPA	50 mg/kg FW one week prior to breeding to parturition in the maternal diet. Both sexes were exposed and examined.	Juvenile and adult BPA-exposed males were more anxious, as evidenced by EPM testing.
Xu et al., 2012 [59]	ICR mice	BPA	0.4 and 4 mg/kg/d from gestational days 7 through 20 to the mother. Both sexes were exposed and examined.	No effect in females. Both BPA-exposed males and females exhibited anxiety- and depressive-like behaviors. However, the effect in the females was more pronounced and consistent across anxiety-testing behavioral tests (open field, dark-light transition task, mirrored maze, and EPM).
Xu et al., 2013 [50]	ICR mice	BPA	0.4, 4, and 40 mg/kg day for 12 weeks during adulthood. Both sexes were treated and examined.	Adult exposure to BPA increased number of times males reared in the Open field maze but reduced this behavior in females. Additionally, exposed males demonstrated impaired spatial and passive avoidance memory, as evidenced when tested in the Morris water maze and footshocks. Similar effects were not observed in BPA-exposed females.
Gioiosa et al., 2013 [60]	CD1 mice	BPA	10 µg/kg bw/day beginning last week of pregnancy through the first week after pregnancy to the mother. Both sexes were exposed and examined.	Females exposed to BPA pre- or post-natally showed increased anxiety behaviors and were less likely to explore novel environments relative to control females. Such effects were not observed in exposed males.
Jones et al., 2012 [62]	Long Evans rats	BPA	5, 50, 500 and 5,000 µg/kg body weight/day from gestational day 7 through post-natal day 14 to the mother. Both sexes were exposed and examined.	Perinatal exposure to BPA eliminated sex differences that existed between control males and females in EPM and Forced Swim Test (FST) where control females generally travel greater distance in the EPM, spending more time being mobile in the EPM and FST, and showed greater rotations than control males.
Kundakovic et al. 2013 [39]	BALB/c mice	BPA	2, 20, and 200 µg/kg body weight/day from gestational day 0 through 19 to the mother. Both sexes were exposed and examined.	Prenatal BPA exposure disrupted normal sexually dimorphic differences in play behaviors, such as chasing. Exposed males were hyperactive; whereas exposed females were hypoactive in the open field-test. Similarly, BPA-exposed males demonstrated decreased anxiety-like behavior. In contrast, BPA exposed females were more anxious.
Williams et al., 2013 [55]	California mice (<i>P. californicus</i>)	BPA	50 mg BPA/kg FW two weeks prior to conception through lactation in the maternal diet. Both sexes were exposed and examined.	Developmental exposure to BPA abolished sex differences for exploratory behavior where control females are more exploratory than control males. BPA-exposed males exhibited decreased territorial marking when a control male was present in the testing arena.
Braun et al., 2009 [63]	Two-year-old children	BPA	Median maternal urinary concentrations: 1.3-1.8 µg/L, as measured at 16 and 26 weeks gestation and at birth. Both sexes were examined.	Linkage of prenatal BPA concentrations (as determined by maternal urinary concentrations during pregnancy) and externalizing behaviors for girls but not boys.

Table 1 (continued)

Publication(s)	Animal model/ human cohort population	EDC(s) tested or correlation analysis performed	Dosing regimen / method to measure BPA concentrations	Major findings
Perera et al., 2012 [64]	Three- to five- year old children	BPA	Median maternal urinary concentrations at 34 weeks gestation: 1.8 µg/L Median child urinary concentrations at 3 to 4 years of age: 3.5 µg/L. Both sexes were examined.	Linkage of prenatal BPA concentrations (as determined by maternal urinary concentrations during pregnancy) and increased emotionally reactive and aggressive behaviors in boys but opposite effect in girls with increased BPA exposure correlated with decreased anxiety and aggressive behaviors.
Harley et al., 2013 [65]	Seven- and nine- year-old children	BPA	Median maternal urinary concentrations: 1.1 µg/L Median child urinary concentrations at 5 years of age: 2.3 µg/L. Both sexes were examined	Linkage of prenatal BPA concentrations (as determined by maternal urinary concentrations during pregnancy) and increased internalizing behaviors in boys, including anxiety and depression at seven years of age. Childhood urinary BPA concentrations positively correlated with increased externalizing behaviors, e.g. conduct problems, in girls at age 7 and increased internalizing, inattention, and hyperactive behaviors in boys and girls at this age.

Male California mice (*Peromyscus californicus*) generally pair-bond with a single female, and thus they do not possess enhanced spatial navigational ability relative to females [54]. Consistently, developmental exposure to BPA or EE has not altered spatial navigation in male or female California mice [55]. However, BPA exposure abolished typical sex differences in the exploratory behaviors of this species, with exposed females spending less time in the open arms of the maze (30 cm platforms lacking barriers on each side, comparable to the animal being placed on a diving board 100 cm above the ground)—a positive index of exploration—than control females and an equivalent amount of time to that of control males.

Although BPA disruptions in exploratory, anxiety-like, and depressive-like behaviors have been found to differ across contrasting species of rodents, a common thread is that BPA exposure reduces sex differences in behaviors. In the deer mice studies described above, BPA or EE exposure during development increased anxiety-like behavior in elevated-plus-maze males but not in females [56, 57]. Similar sexually dimorphic responses were seen in C57BL6J mice, as developmental BPA exposure increased anxiety-like behavior in males but not in females [58]. In both of these species, control females showed higher levels of anxiety-like behavior than males. In contrast, studies with ICR, BALB-c, and CD1 mice reported that developmental BPA exposure increased anxiety-like behavior in females but not in males [59–61]. Similar disruptions of typical sexually dimorphic differences in exploratory behaviors have been reported in Long-Evans rat females exposed to BPA during the perinatal period [62]. In all four strains, control males showed higher levels of anxiety like behavior than females.

In humans, the primary neurodevelopmental types of outcomes associated with increased maternal or childhood urinary BPA concentrations have been emotional behaviors. One study reported that elevated maternal urinary BPA concentrations between 16 weeks of gestation and birth were linked to increased externalizing behaviors (e.g., hyperactivity and aggression) in girls but not in boys at 2 years of age [63]. The absence of an effect in boys might be related to the developmental stage that was examined. Another epidemiological study focusing on older children (3–5 years of age) reported that higher maternal BPA concentrations in urine at 34 weeks of gestation and higher child urinary BPA concentrations were associated with increased externalizing behaviors in boys, whereas the opposite correlation was reported in girls [64]. Examination of children at even later ages (7- to 9-year-olds) also demonstrated trends for an interaction between prenatal BPA exposure and externalizing problems, with higher BPA concentrations being linked to increased externalizing problems in boys but not in girls [65]. Externalizing problems in boys become more prevalent at 5–7 years of age, which may partially explain why the effects of BPA on externalizing

problems were observed only in studies with older children [66]. Other environmental factors are also likely to be important, as there was variability across the studies in socioeconomic status. All of the studies reviewed above considered internalizing problems as well, but there was little consistency in how these problems were associated with BPA across the studies. It is not clear whether these differences are due to intrinsic sex-specific behavioral vulnerabilities to environmental factors or whether BPA is accentuating already existing sexually dimorphic behavioral differences.

BPA exposure disrupts several sociosexual behaviors in various rodent models. In mate choice experiments, both BPA and control female deer mice preferred control males over males that had been developmentally exposed to BPA [24••]. Male California mice must defend their territory and their mate from male intruders by engaging in territorial marking. However, BPA-exposed California male mice exhibited suppressed territorial marking when control males were present in the test arena [55]. Prenatal exposure of BALB-c mice disrupted normal sexually dimorphic differences in play behavior [39]. It remains to be determined whether these behavioral changes equate to altered male reproductive success. It is also not clear how well the various sex-specific behavioral differences will translate to humans.

Another concern relates to potential differences in metabolism of BPA between rodents and humans. Both adult rodents and primates primarily metabolize BPA through glucuronidation of BPA via UDP-glucuronosyltransferases (UGTs). However, clearance of BPA in primates is generally through urinary excretion, whereas the biliary–fecal route is the primary route of excretion in rodents [67, 68]. Other potential pharmacokinetic differences across species include metabolism of BPA through sulfonation, which is generally minor in adult animals [69–71], and enterohepatic recirculation of BPA, which occurs to a minor extent in rodents and even less in primates [72, 73]. Importantly, a side-by-side analysis of serum BPA concentrations in mice and rhesus monkeys (*Macaca mulatta*), who were both given a comparable oral bolus, demonstrated that the clearance of BPA was comparable in the two species [73]. Thus, even though there are minor differences in the pharmacokinetics of BPA metabolism between rodents and primates, findings in rodents are almost assuredly applicable to primates, including humans [73–75].

While BPA weakly binds to ESR1 and ESR2, it is not clear if all of the above sex-specific behavioral differences are due to engaging these steroid receptors. This chemical can also bind to other steroid and non-steroid receptors, such as thyroxine receptor (TR), AR, glucocorticoid receptor (GR), peroxisome proliferator-activated receptor (PPAR), and pregnane X receptor [43, 76–79].

Other Endocrine-Disrupting Compounds

It is beyond the scope of this review to cover all of the EDCs that are proposed to disrupt sexually dimorphic behaviors in various animal models. Table 2 provides a comprehensive list of other EDCs and their impact on the above behavioral categories. Three types of examples are (1) the estrogenic compounds EE, estrogen present in birth control pills, and diethylstilbestrol (DES), which was administered from the 1950s to the 1970s under the misconception that it prevented miscarriages; (2) the androgenic compounds testosterone, 17 α methyl dihydrotestosterone (MDHT), and levonorgestrel, and the antiandrogenic class, exemplified by flutamide; and (3) a broad range of other EDCs, including insecticides, such as methoxychlor (MXC) and dichlorodiphenyltrichloroethane (DDT) and its active metabolite, dichlorodiphenyldichloroethylene (p,p-DDE), fungicides (especially vinclozolin, which has antiandrogenic properties), plasticizers [e.g., di(2-ethylhexyl) phthalate (DEHP)], and coolants/insulating fluids (e.g., polychlorinated biphenyls [PCBs]). Even some commonly used antimicrobials, such as triclosan and triclobarban, may exert endocrine disrupting properties. The two illustrative chemicals, EE and vinclozolin, where across taxa sex-specific disruptions have been reported, will be further discussed.

Effects of EE on sex-specific behaviors have been documented in a wide range of species, including rodents, fish, pipefish, frogs, and birds, as detailed above (for *Peromyscus* species, where BPA was tested alongside EE, as required by current FDA guidelines for BPA studies) and below. Sand goby (*Pomatoschistus minutus*) males exposed to EE as adults become demasculinized, as evidenced by their protracted time to engage in nest-building, compromised courtship behaviors, diminished aggressive behaviors, and altered parental care relative to control males [80, 81]. Gulf pipefish (*Syngnathus scovelli*) possess sex-role reversal in that females must compete for a limited number of males to carry fertilized eggs. However, EE-treated males exhibited female-like secondary sexual traits, and mate choice trials have revealed that females, which are typically not the choosier sex in this species, selectively reject these males [82]. African clawed male frogs exposed as adults to EE display reductions in the number of and temporal/spectral qualities in advertisement calls and demonstrate elevated number of rasping calls [83]. Moreover, females selectively reject these males in mate choice trials. In ovo exposure of Japanese quail (*Coturnix japonica*) to EE leads to later depression of male sexual behaviors [84]. Taken together, the cross-species findings provide robust evidence that developmental and adult exposure to EE compromises later male sexual behaviors and attractiveness to females across taxa.

The antiandrogenic compound vinclozolin has been reported to disrupt sexually dimorphic behaviors in fish, frogs, and

Table 2 Example animal model linking other EDC exposure and sex-specific behavioral alterations

Publication	Animal model	EDC(s) tested or correlation analysis performed	Dosing regimen	Major findings
Bertolasio et al., 2011 [163]	Sprague–Dawley rats	MXC and E2	2.0 mg MXC and 10 mg E2 on post-natal days 1, 3, and 5. Only females treated.	Perinatal exposure to MXC and E2 combined led to adult females demonstrating suppressed proceptive behaviors and increased rejection of males.
Carbone et al., 2013 [164]	Wistar rats	Di-2-ethylhexyl phthalate (DEHP)	30 mg/kg/bw/day from postnatal 1 to weaning. Both males and females were treated.	Perinatal DEHP exposure increased anxiety-like behaviors (decreased open arm entries and time spent in the open arms of the EPM and increased time spent in the closed arms); whereas, no effect was observed in exposed females.
Hotchkiss et al., 2003 [87]	Sprague–Dawley rats	Vinclozolin, flutamide, and testosterone propionate	Vinclozolin (50 mg/kg/day) or testosterone propionate (TP, 250 µg/kg/day) were administered at postnatal days 2 and 3. Both sexes were treated.	Perinatal exposure to vinclozolin or flutamide decreased social play behaviors in juvenile males to approach control female levels. When neonatal testosterone-treated females were tested as juveniles, they demonstrated increase (masculinized response) in these same play behaviors.
Baattrup et al., 2001 [85]	Guppy fish (<i>Poecilia reticulata</i>)	Vinclozolin, p,p-DDE, and flutamide	Adults were treated for 30 days with these three chemicals in the fodder at concentrations between 0.1 and 100 µg/g/fodder. Only males were treated.	Adult exposure of males to all three of the chemicals resulted in discoloration with reduced sexually attractive orange-yellow areas and severe reduction in courtship behaviors.
Schultz et al., 2012 [165]	Fathead minnow (<i>Pimephales promelas</i>)	Triclosan (TCS) and triclobarban (TCC)	Newly hatched and adult fathead minnows were exposed for 12 and 21 days, respectively, to TCC (1.6 µg/L) or a mixture (560 ng/l TCS + 179 ng/L TCC and 1.6 µg/L TCS + 450 ng/L TCC). Both sexes were treated.	Adult exposure of males to triclosan or the combination of triclosan and triclobarban led to decreased aggression.
Knapp et al., 2011 [166]	Mosquitofish (<i>Gambusia affinis</i>)	Cortisol	Experiment 1: cortisol treatments were 0.5, 1.0 or 2.0 mg/L, Experiment 2 cortisol treatments were 0.05, 0.1 or 0.5 mg/L. Only females were tested.	Developmental exposure of females to cortisol resulted in adult male-typical anatomical structures (elongated anal fins with distal tip features) and demonstrated masculinized male reproductive behaviors, including attempting to copulate with control females.
Saaristo et al., 2010 [80]	Sand gobies (<i>Pomatoschistus minutus</i>)	EE	Chronic adult exposure (1 to 4 weeks) to EE (11 ng/L). Only males were treated.	Adult EE exposed males took longer to build a nest, had decreased courtship and leading behaviors, and were less aggressive than control males.
Saaristo et al., 2010 [81]	Sand gobies (<i>Pomatoschistus minutus</i>)	EE	Adult exposure for 10 to 31 days to EE (41 ng/L)	Adult exposure to EE led to altered parental care by males, as evidenced by increased fanning behavior of the eggs relative to controls.
Partridge et al., 2010 [82]	Gulf pipefish (<i>Syngnathus scovelli</i>)	EE	Adult exposure to 1 ng EE/L or 100 ng EE/L for 10 days. Only males were treated.	This species is sex-role reversed with sexual selection acting more strongly on females than males and females competed for the limited number of males. However, adult EE exposure results in males exhibiting female-like secondary sexual traits. Even though these exposed males are capable of reproduction, females discriminate against them in mate choice trials.
Hoffmann et al., 2012 [83]	African clawed frogs (<i>Xenopus laevis</i>)	EE	Adults exposed to EE (0.296 ng/L, 2.96 ng/L, 29.64 ng/L, 2.96 µg/L and 296.4 µg/L) for 96 hours. Only males were tested.	Adult exposure of males to EE lowered male sexual arousal, as evidenced by decreased proportion and temporal/spectral parameters of advertisement calls and increased proportion of rasping calls (indicative of an unaroused male). Mate choice experiments demonstrated that females found exposed males less sexually attractive.

Table 2 (continued)

Publication	Animal model	EDC(s) tested or correlation analysis performed	Dosing regimen	Major findings
Hoffmann et al., 2010 [86]	African clawed frogs (<i>Xenopus laevis</i>)	Vinclozolin	Adults exposed to Vinclozolin at concentrations ranging from 10 ⁻⁶ to 10 ⁻¹⁰ M for 96 hours. Only males were treated.	Adult exposure of males to vinclozolin (10 ⁻⁶ M) decreased advertisement calls and chirping and increased proportion of rasping calls.
Frederick et al., 2011 [167]	American white ibises (<i>Eudocimus albus</i>)	Methylmercury (MeHg)	Three year treatment of adults to MeHg (0.05 to 0.3 ppm wet weight). Both males and females were treated.	Long term exposure (3 years) resulted in increased proportion of males pair-bonding with males and decreased male courtship behavior to females and affected female sexual preference with courting females approaching exposed males less than control males. Exposed females demonstrated decreased egg productivity.
Halldin et al., 1999 [84]	Japanese quail (<i>Coturnix japonica</i>)	EE and diethylstilbestrol (DES)	<i>In ovo</i> treatment to EE (6 ng/g) or DES (19 ng/g). Both sexes were treated but only males were further studied.	<i>In ovo</i> exposure to EE and DES resulted in depressed male sexual behavior.

rodents. In guppy fish (*Poecilia reticulata*), males exposed as adults to this chemical possessed less sexually attractive orange-yellow coloration and suppression of male-typical courtship behaviors [85]. Male African clawed frogs (*Xenopus laevis*) exposed as adults to vinclozolin demonstrated a decreased proportion of advertisement calls and chirping (indicative of an aroused state) and an increased proportion of rasping calls (indicative of a non-aroused state) [86]. Perinatal exposure to vinclozolin or flutamide eliminates male-typical social play behaviors in Sprague Dawley juvenile male rats [87].

Sexually Dimorphic Behavioral Differences in Psychosocial Stress

Just as the effects of EDC depend on developmental timing, the effects of psychosocial stress on the brain and behavior also depend on the stage of development. Intriguingly, when the mother is exposed to psychosocial stress during pregnancy, stronger effects are observed in male offspring, whereas the effects of psychosocial stress during adolescence or after sexual maturity are usually stronger in females.

Early Life Stress

Early life stress induces long-lasting changes in a diverse set of metabolic and neurobiological systems [88]. The effects of psychosocial stress early during gestation usually have more long-lasting consequences than the effects of stress later in gestation. For example, when pregnant female mice were exposed to chronic variable stress, male but not female offspring spent more time floating in the forced swim test [89]. Floating in this test is considered to be a measure of behavioral despair because drugs with antidepressant properties reduce floating and increase swimming [90]. Although many physiological systems are affected by psychosocial stress, the impact of elevated glucocorticoids has been best studied. When rat dams were injected with corticosterone during pregnancy, male but not female adolescent offspring showed increased anxiety-like behavior [91]. Corticosterone injections during pregnancy also increased floating behavior in the forced swim test in both male and female adolescent offspring. On average, it appears that males are more sensitive to glucocorticoids during prenatal development, which is consistent with the findings from clinical studies reporting that maternal depression during or after pregnancy has stronger effects on anxiety in boys than in girls [92]

Increased corticosterone levels in the mother can also impact postnatal development. Dams injected with corticosterone have increased corticosterone levels in breast milk, as well as increased brain levels of corticosterone in their pups [93]. Males but not females had suppressed neurogenesis in

the hippocampus [94], which is thought to be an important mechanism conferring resilience to the long-term effects of stress [95]. In this study, postnatal corticosterone exposure had no effects on behavior in the forced swim test, which is a short-term behavioral response. Future studies could also consider the impact of postnatal corticosterone exposure on longer-lasting stressors, such as chronic variable stress or social defeat.

Adolescence appears to be an important transition with regard to sex differences in sensitivity to psychosocial stress [96]. In adolescent rats, a combination of social and physical stressors increased depression-like behaviors in females but not in males [97]. Adolescent stress also increases behavioral sensitivity to drugs of abuse, and this effect is stronger in female rats than in males [98]. These results suggest that females have increased physiological responses to psychosocial stress during adolescence. These findings are also consistent with epidemiological work supporting the hypothesis that girls are more likely than boys to carry risk factors for stress-induced mental disorders (such as depression), and that the challenges of adolescence engage these risk factors to impact mental health [99, 100].

Chronic Mild Stress

The chronic mild stress (CMS) paradigm has become a widely used approach to induce behavioral phenotypes associated with depression. CMS consists of a combination of physical and low-level social stressors administered in an unpredictable order [101]. Examples of stressors include changes of cage mates, exposure to cold temperatures, and disruption of light cycles. One of the most common responses to CMS is anhedonia, or reduced interest in rewards, such as sucrose, high-fat food, or sex. Reduced motivation to obtain reward is a key component of depression [102]. Consumption of preferred food items, such as sucrose, generates hedonic behavioral responses, which are evolutionarily conserved [103]. There have been concerns that reduced sucrose intake could be induced by stress-induced weight loss rather than by anhedonia per se [104]. While stress-induced weight loss can be included as a covariate statistically [105], some laboratories have been unable to replicate the effects of CMS on sucrose intake [106, 107]. An intriguing alternative approach is examination of more ethological measures of behavior. For example, several lab groups have observed that CMS reduces male sexual behavior in rats [108–110]. Although more study is needed, it will be interesting to see if the effects of CMS on sexual behavior are more robust than the effects on food/taste preferences.

The overwhelming majority of CMS studies have focused on males, but a few have examined females [111]. In general, CMS reduced sucrose consumption in both males and females. While stress-induced anhedonia is usually stronger in

females [112–114], some studies have reported that males and females are equally affected [115, 116]. This inconsistency suggests that the use of more ethological approaches, such as sexual behavior, could be useful. The effect of social isolation on anhedonia has also been reported to induce stronger responses in females [117]. However when male and female rats were challenged with a novel stressor (the forced swim test), females exposed to CMS engaged in more floating behavior (considered to be an index of behavioral despair), whereas males engaged in less floating behavior [112]. To our knowledge, no study has examined whether CMS impairs female sexual behavior. Mixed results have been reported on the effects on CMS on the hypothalamic–pituitary–adrenal (HPA) axis. The most common result is that CMS increases baseline corticosterone levels, which has been reported in both males [107, 112, 118, 119] and females [114]. However, other reports have noted no effects of CMS on corticosterone levels [116, 120–122]. Divergent results may be a result of genetic variability across genetic lines. There is substantial variation in coping responses between the different lines of rats [123]. Some lines respond to stress with reactive coping strategies, consisting of behavioral responses such as immobility. Other lines respond with more proactive coping strategies, such as escape. Individuals using more reactive coping strategies are more likely to have higher stress-induced glucocorticoid levels than individuals using more proactive strategies [124].

Social Stress

A powerful source of stress in many species comes from competitive interactions and aggression. Interestingly, many of the behavioral and neurobiological phenotypes observed in individuals that lose aggressive encounters are evolutionarily conserved [125, 126]. One of the most widely reported phenotypes induced by defeat stress is withdrawal from social contexts, even non-threatening contexts [127, 128]. Social withdrawal has special relevance for mental health, because patients diagnosed with depression show stronger avoidance responses to social cues [129, 130]. Social avoidance further reduces social support and helps to maintain depression [131]. Like CMS, defeat stress induces reduced intake of sucrose [132, 133]. Scent marking can also be used to estimate sexual motivation, and this behavior is strongly inhibited by defeat stress [134]. Defeat stress has proven to be a robust approach, as many behavioral phenotypes have been replicated in different lab groups and species [125]. One drawback, however, is that it has been very difficult to study sex differences, because female rats and mice are generally not aggressive toward other females. However, creative use of different species or manipulations of context have allowed several groups to study defeat stress in females.

Under certain conditions, lactating female rats will engage in aggression toward other females. Variability between

different rat strains may be an important factor influencing the intensity of defeat. Sprague Dawley dams appear to have lower aggression levels, and females exposed to defeat by a dam actually had decreased levels of floating behavior in the forced swim test, compared with controls [135]. In contrast, Wistar dams appear to have higher aggression levels, and females exposed to defeat showed increased floating in the forced swim test and sucrose anhedonia [136]. Long–Evans dams also appear to be more aggressive, and females exposed to defeat showed increases in depression-like behaviors [137] and increased self-administration of cocaine [138]. This approach represents a significant advance because it allows for the study of defeat stress in a species in which there is a strong literature in males. However, given the relatively low aggression levels of dams toward other females, it is harder to directly compare males and females. Other rodent species such as Syrian hamsters (*Mesocricetus auratus*) and California mice (*Peromyscus californicus*) allow for more direct comparisons of males and females because their intrafemale aggression levels are higher and females will engage in aggression in the absence of pups. Intriguingly, female Syrian hamsters appear to be more resistant to the behavioral effects of defeat stress than males [139], and this resistance appears to be mediated in part by circulating estradiol [140]. In California mice, defeat stress has very different long-term effects on behavior and the HPA axis in males and females.

The California mouse is a monogamous species, in which both males and females defend a territory. Female California mice are aggressive in resident–intruder tests [141], which facilitates the use of social defeat in both males and females. Acute responses of the HPA axis are more sensitive to social conflict in females than in males. Females show a significant increase in corticosterone following a resident–intruder test, and this increase is observed in both residents (winners [142]) and intruders (losers [143]). In contrast, neither male residents nor intruders show an increase in corticosterone. This sex difference in corticosterone responsiveness is mediated by gonadal hormones (Fig. 1a). Castration sensitizes male corticosterone responses to defeat stress, whereas ovariectomy blocks defeat-induced increases in corticosterone in females [143]. Notably, the long-term effects of defeat stress on baseline corticosterone are quite different. Defeat stress increases male baseline corticosterone during both the active phase and the inactive phase, but has no effect on females [144••], which is similar to findings in female rats [135]. Elevated corticosterone during the inactive phase is often observed in patients diagnosed with depression, and some recent reports have suggested that this symptom is more likely to occur in men [145, 146]. While defeat stress has a stronger effect on baseline corticosterone levels in males, defeat stress has a stronger effect on social interaction behavior in female California mice.

Male and female California mice are highly motivated to approach unfamiliar individuals, like many other strains of *Mus* [147]. However, social defeat reliably reduces social

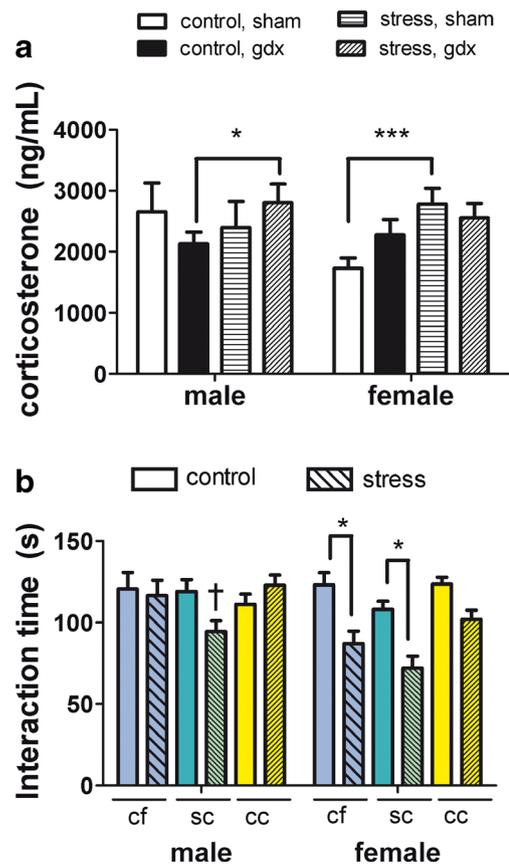


Fig. 1 Effects of social defeat on corticosterone (a) and social interaction (b) behavior in California mice. Social stress increases corticosterone levels in female California mice, and ovariectomy blocks this effect. In contrast, castrated males have increased corticosterone levels following stress. The effect of defeat stress on social interaction is stronger in females than in males, but the effect is weaker in females raised on corn cob bedding. * $p < 0.05$ versus control, *** $p < 0.001$ versus control, † $p < 0.05$ male versus female. cc corn cob, cf cardboard bedding, Gdx gonadectomy, sc woodchip bedding

approach in female California mice, whereas this effect is weaker or absent in male California mice [144••, 148]. This result mimics reports in humans that social withdrawal occurs to a greater degree in women with depression than in men [149]. Unlike the effects of defeat stress on corticosterone, there is no effect of gonadectomy on social interaction behavior [143]. Similarly, social withdrawal is observed across different stages of the estrous cycle [144••]. These results suggest a diminished role for gonadal hormones in mediating sex differences in social withdrawal behavior in adults. However, there is evidence that hormones may have more important effects early in life. This evidence comes from an unexpected finding that cage bedding has important effects on behavioral responses to stress (Fig. 1b). Corn cob bedding contains tetrahydrofuran (THF) diols, which have estrogenic properties but do not bind directly to ESRs [150]. California mice raised on corn cob have significantly elevated levels of THF diols [151], most likely through consumption of

bedding. When female California mice were raised on corn-cob bedding, the effect of defeat stress on social interaction behavior was blunted, compared with females raised on aspen wood chips or cardboard-based bedding [143]. This finding suggests that females raised on corn-cob could be masculinized during development. Interestingly, THF diols stimulate cyclooxygenase (COX)-2 activity [152]. In male rats, estradiol increases COX2 activity to increase production of prostaglandins in the preoptic area (POA) of the hypothalamus [153]. Prostaglandins induce the formation of dendritic spines in the POA, which are more abundant in males than in females and are thought to play an important role in controlling male sexual behavior [154].

Conclusions

Developmental/adult exposure to EDCs—in particular, BPA—is associated with sex-specific effects in various animal models and human epidemiological studies. Across animal models, male sexually selected traits that affect intrasexual competition and intersexual choice appear to be especially vulnerable to the EDCs that have been tested to date. EDCs also seem to exert sex-specific effects on anxiety/depressive-like behaviors in animal models and human epidemiological studies [24•, 39, 49, 58–60, 63–65]. While only a handful of studies have directly assessed linkages between BPA exposure and sex-specific behavioral differences in humans, a somewhat consistent finding is that prenatal BPA exposure is linked to increased externalizing behavioral problems, particularly in older boys [63–65]. However, future studies are needed to clarify whether early BPA exposure alters neurobehavioral programming in animal models and humans, and whether the observed differences persist with maturity.

EDCs likely exert sex-specific behavioral effects by disrupting normal steroid programming of the brain, which could occur through direct binding of neural steroid receptors [155–157], modulation of steroid hormone synthesis or metabolism [156–158], and/or epigenetic alterations of steroid-dependent genes [159]. These changes likely shape how an individual reacts to challenges faced later in life.

The effects of psychosocial stress are also dependent on the developmental stage, with males exhibiting increased vulnerability during the prenatal stage and females exhibiting increased sensitivity in adolescence. In adults, the effects of psychosocial stress are sex dependent. For example, defeat stress induces social withdrawal in females and disrupts baseline corticosterone levels in males.

Future studies should thus consider the combined impact of early exposure to an EDC, such as BPA, and later life stress (the “two-hit” model) on sex-specific behaviors. It is clear that BPA can induce anxiogenic effects, which vary according to the sex.

However, the interaction between BPA exposure and psychosocial stress is still unclear. It will be essential to disentangle direct effects of BPA on brain development from indirect effects of BPA that may be mediated by altered parental behavior. BPA reduces hypothalamic GR expression [160], which might exaggerate glucocorticoid responses to stress. It has also been suggested that BPA can directly bind and activate GR [77], which would be another avenue by which BPA can affect later social and environmental stressors [161].

In conclusion, behaviors such as sexually selected traits might serve as a barometer of exposure to EDC or psychosocial stress. An important implication of sex-specific disruptions in behavior is the long-term impact on susceptibility to stress later in life. There are important sex differences in behavioral and neurobiological responses to stress [125, 162], and at least some of these differences originate from early life experience. Thus exposure to EDC early in life is likely to alter sex-specific responses to stress in adults. However, to our knowledge, there has been no study to date aimed at testing this novel hypothesis that developmental exposure to EDCs followed by later social/environmental stressors can lead to harmful biomolecular and behavioral changes that are sex dependent. Therefore, future studies are needed to determine the potential combined epigenetic and gene expression effects that these extrinsic factors exert on the various brain regions governing adult cognitive and sociosexual behaviors and whether the neurobehavioral responses vary according to sex.

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Compliance with Ethics Guidelines

Conflict of Interest Cheryl S. Rosenfeld and Brian C. Trainor declare that they have no conflict of interest.

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