Review

Sex Differences in Vulnerability and Resilience to Stress Across the Life Span

Georgia E. Hodes and C. Neill Epperson

ABSTRACT

Susceptibility and resilience to stress depend on 1) the timing of the exposure with respect to development, 2) the time across the life span at which effects are measured, and 3) the behavioral or biological phenotype under consideration. This translational review examines preclinical stress models that provide clues to causal mechanisms and their relationship to the more complex phenomenon of stress-related psychiatric and cognitive disorders in humans. We examine how genetic sex and epigenetic regulation of hormones contribute to the proximal and distal effects of stress at different epochs of life. Stress during the prenatal period and early postnatal life puts male offspring at risk of developing diseases involving socialization, such as autism spectrum disorder, and attention and cognition, such as attention-deficit/hyperactivity disorder. While female offspring show resilience to some of the proximal effects of prenatal and early postnatal stress, there is evidence that risk associated with developmental insults is unmasked in female offspring following periods of hormonal activation and flux, including puberty, pregnancy, and perimenopause. Likewise, stress exposures during puberty have stronger proximal effects on girls, including an increased risk of developing mood-related and stress-related illnesses, such as depression, anxiety, and posttraumatic stress disorder. Hormonal changes during menopause and andropause impact the processes of memory and emotion in women and men, though women are preferentially at risk for dementia, and childhood adversity further impacts estradiol effects on neural function. We propose that studies to determine mechanisms for stress risk and resilience across the life span must consider the nature and timing of stress exposures as well as the sex of the organism under investigation.

Keywords: CRF, Epigenetics, Estrogens, Mood disorders, Sex differences, Stress
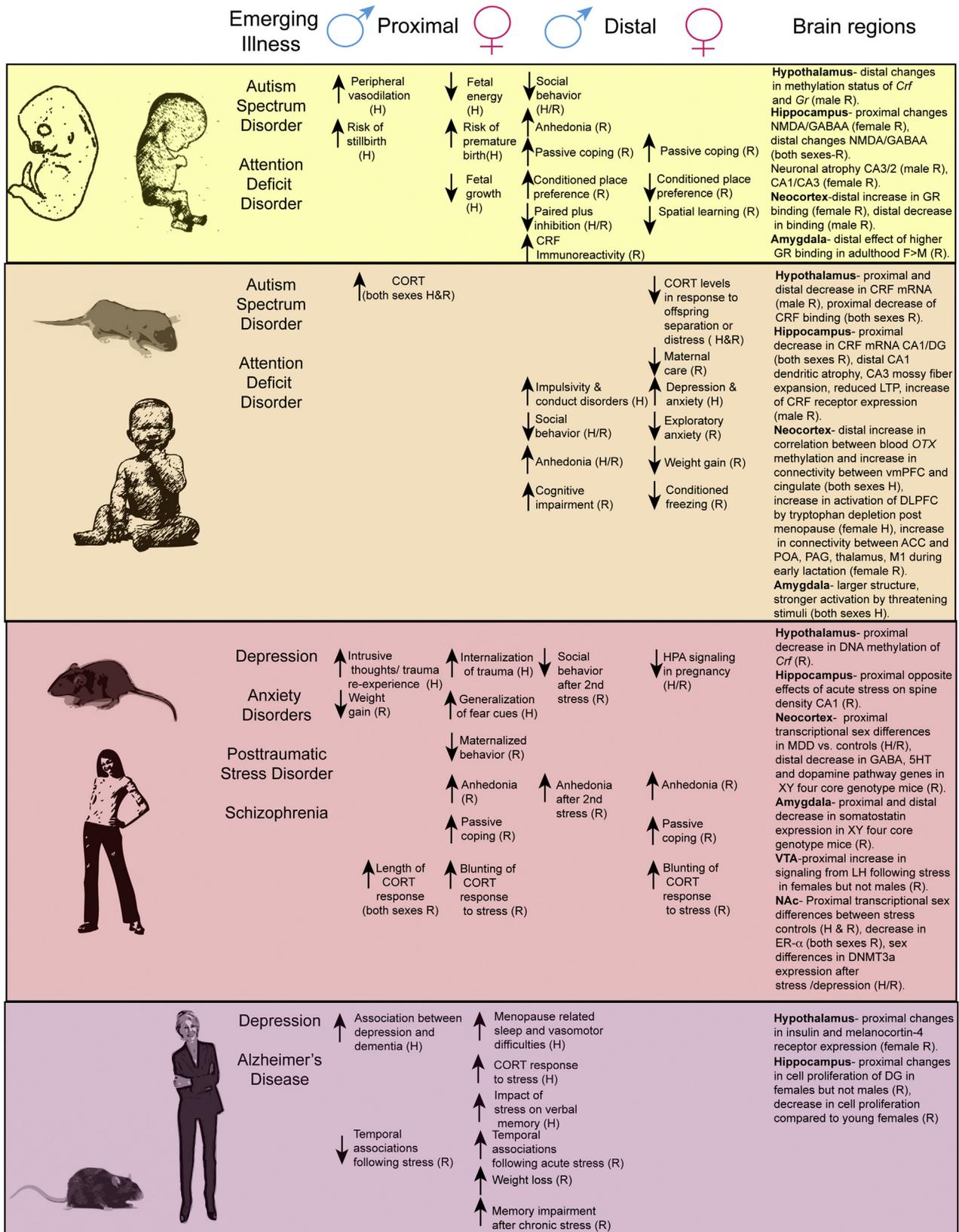
https://doi.org/10.1016/j.biopsych.2019.04.028

How do we define resilience to stress? In preclinical models, resilience is ascribed to animals that experience a stressor, yet demonstrate biological or behavioral phenotypes similar to unstressed control animals. In clinical research, the ability to experience significant stress without subsequent psychopathology is considered a sign of resilience. However, studies of immune, hypothalamic-pituitary-adrenal (HPA) axis, and brain function suggest that such exposures have a physiologic impact even in asymptomatic individuals (1–3). Such alterations create risk for adverse health conditions later in life. The fact that many individuals experience psychopathology in the setting of acute stress and fully recover highlights the complexity of risk and resilience research in humans.

In research using rodent, primate, and human subjects, biological and behavioral adaptations in response to stress along with nurturing environments mitigate the adverse effects of significant stress (4–8). Preclinical studies indicate that milder, repeated stress or being housed in a nurturing environment leads to epigenetic and neurohormonal profiles associated with less behavioral dysregulation later in life, even when exposed to additional stressors. Support from family and the wider social environment at the time of trauma exposure and throughout life is critical to promoting resilience in humans (8).

Studies that use stress to induce behavioral endophenotypes focus mostly on proximal effects. However, most psychiatric disorders have prodromes that can appear years before the individual reaches symptom threshold for psychiatric illness (9,10). The events that contribute to the occurrence of the disorder may also occur years before the emergence of frank symptoms (11). Finally, most basic research examining the mechanisms of resilience has been done in only male animals (12), whereas most humans experiencing stress-related disorders are female (13,14).

We examine here the concept of resilience as both a proximal and a distal response to stress. Proximal responses are defined as those that occur within the same developmental epoch as the stress exposure, and distal responses as those that occur within a subsequent developmental epoch. Similar measurable end points from basic and clinical research examining sex differences in vulnerability and resilience of response to stress across the life span are highlighted (Figure 1). We propose that resilience is an active and dynamic process that is shaped in part by genetic sex, gonadal

Emerging Illness	♂ Proximal ♀	♂ Distal ♀	Brain regions
Autism Spectrum Disorder **Attention Deficit Disorder**	♂: ↑ Peripheral vasodilation (H); ↑ Risk of stillbirth (H) ♀: ↓ Fetal energy (H); ↑ Risk of premature birth (H); ↓ Fetal growth (H)	♂: ↓ Social behavior (H/R); ↑ Anhedonia (R); ↑ Passive coping (R); ↑ Conditioned place preference (R); ↑ Paired plus inhibition (H/R); ↑ CRF Immunoreactivity (R) ♀: ↑ Passive coping (R); ↓ Conditioned place preference (R); ↓ Spatial learning (R)	**Hypothalamus**- distal changes in methylation status of *Crf* and *Gr* (male R). **Hippocampus**- proximal changes NMDA/GABAA (female R), distal changes NMDA/GABAA (both sexes-R). Neuronal atrophy CA3/2 (male R), CA1/CA3 (female R). **Neocortex**-distal increase in GR binding (female R), distal decrease in binding (male R). **Amygdala**- distal effect of higher GR binding in adulthood F>M (R).
Autism Spectrum Disorder **Attention Deficit Disorder**	♂: ↑ CORT (both sexes H&R) ♀: ↑ Impulsivity & conduct disorders (H); ↓ Social behavior (H/R); ↑ Anhedonia (H/R); ↑ Cognitive impairment (R)	♀: ↓ CORT levels in response to offspring separation or distress (H&R); ↑ Maternal care (R); ↑ Depression & anxiety (H); ↑ Exploratory anxiety (R); ↑ Weight gain (R); ↓ Conditioned freezing (R)	**Hypothalamus**- proximal and distal decrease in CRF mRNA (male R), proximal decrease of CRF binding (both sexes R). **Hippocampus**- proximal decrease in CRF mRNA CA1/DG (both sexes R), distal CA1 dendritic atrophy, CA3 mossy fiber expansion, reduced LTP, increase of CRF receptor expression (male R). **Neocortex**- distal increase in correlation between blood *OTX* methylation and increase in connectivity between vmPFC and cingulate (both sexes H), increase in activation of DLPFC by tryptophan depletion post menopause (female H), increase in connectivity between ACC and POA, PAG, thalamus, M1 during early lactation (female R). **Amygdala**- larger structure, stronger activation by threatening stimuli (both sexes H).
Depression **Anxiety Disorders** **Posttraumatic Stress Disorder** **Schizophrenia**	♂: ↑ Intrusive thoughts/ trauma re-experience (H); ↓ Weight gain (R); ↑ Length of CORT response (both sexes R) ♀: ↑ Internalization of trauma (H); ↑ Generalization of fear cues (H); ↓ Maternalized behavior (R); ↑ Anhedonia (R); ↑ Passive coping (R); ↑ Blunting of CORT response to stress (R)	♂: ↓ Social behavior after 2nd stress (R); ↑ Anhedonia after 2nd stress (R) ♀: ↓ HPA signaling in pregnancy (H/R); ↑ Anhedonia (R); ↑ Passive coping (R); ↑ Blunting of CORT response to stress (R)	**Hypothalamus**- proximal decrease in DNA methylation of *Crf* (R). **Hippocampus**- proximal opposite effects of acute stress on spine density CA1 (R). **Neocortex**- proximal transcriptional sex differences in MDD vs. controls (H/R), distal decrease in GABA, 5HT and dopamine pathway genes in XY four core genotype mice (R). **Amygdala**- proximal and distal decrease in somatostatin expression in XY four core genotype mice (R). **VTA**-proximal increase in signaling from LH following stress in females but not males (R). **NAc**- Proximal transcriptional sex differences between stress controls (H & R), decrease in ER-α (both sexes R), sex differences in DNMT3a expression after stress /depression (H/R).
Depression **Alzheimer's Disease**	♂: ↑ Association between depression and dementia (H); ↓ Temporal associations following stress (R) ♀: ↑ Menopause related sleep and vasomotor difficulties (H); ↑ CORT response to stress (H); ↑ Impact of stress on verbal memory (H); ↑ Temporal associations following acute stress (R); ↑ Weight loss (R); ↑ Memory impairment after chronic stress (R)		**Hypothalamus**- proximal changes in insulin and melanocortin-4 receptor expression (female R). **Hippocampus**- proximal changes in cell proliferation of DG in females but not males (R), decrease in cell proliferation compared to young females (R)

steroids, and epigenetic regulation of stress physiology and changes across epochs.

PRENATAL STRESS SHAPES AN INDIVIDUAL'S RESPONSE TO THE ENVIRONMENT

The prenatal experience shapes an individual's brain, body, and behavior for their lifetime and potentially even affects the response of subsequent generations through transgenerational mechanisms. Human offspring exposed to extreme gestational stress in the form of maternal starvation during the Dutch Hunger Winter had increased risk of psychiatric disorders, including affective disorders [15], addiction [16], and schizophrenia [17]. Effects of famine were also associated with increased risk of schizophrenia in a separate Chinese population [18]. In humans, it is difficult to separate the effects of maternal psychological distress due to famine from calorie and nutrient restriction, which can have multiple physiologic effects on the offspring, including activation of the HPA axis. Most data have been collected from famine situations, but even maternal immune activation, which induces sickness behavior, results in temporary decreased food intake [19,20]. The flexibility of fetal female energy consumption in response to stress or inflammation may confer proximal protection. Female fetal, but not male fetal, growth is restricted by in utero exposure to maternal uncontrolled asthma [21], a chronic medical condition associated with maternal hypertension, poor oxygenation, heightened immune activation, and risk for preeclampsia [22]. It has been proposed that the ability of the female fetus to respond to an adverse maternal environment is protective against fetal stillbirth, which is higher in male fetuses exposed to maternal asthma and other medical adversities such as preeclampsia [23–25]. Male risk bias is thought to be secondary to male adaptations in placental blood flow allowing the male fetus to continue to grow in utero but be born with greater peripheral vasodilation, a condition associated with worse neonatal outcome [22]. However, the timing of the stress exposure during gestation also contributes to sex differences in its impact. Acute early gestational stress in humans caused by experiencing an earthquake (2–3 months after conception) increased the rate of preterm birth to a greater degree in female offspring [25].

Maternal immune activation in humans mirrors the physiologic effects found during extreme stress and has been linked to increased risk of schizophrenia and autism spectrum disorder [26–30]. Similarly, rodent models of maternal immune activation or stress demonstrate lasting effects predominantly on male offspring behavior [30–33], although effects are also reported in female offspring (Table 1) [34–37]. There is evidence of greater distal effects of prenatal stress in female offspring on subsequent stress-related behavior

and physiology responses later in life [38]. Later gestational stress or cytokine exposure (prepartum day [PPD] 11 to parturition) leads to greater behavioral changes in female offspring than male offspring (Table 1) [39–41]. Translating findings from rodents to humans is complicated for obvious reasons but is also made more complex by the asynchrony between developmental epochs between species. Particularly, the effects of gestational stress are difficult to translate from human to rodent, as rodent parturition occurs at roughly the equivalent of the end of the human second trimester [42].

POTENTIAL MECHANISMS FOR INTERGENERATIONAL TRANSMISSION OF STRESS: CONSIDERATION OF IN UTERO ADAPTATION BY SEX

Initially, female development was characterized as a passive default. However, preclinical research suggests that female brain development is an active process regulated by DNA methylation [43], an epigenetic process through which genetic transcription is silenced [44]. Female fetuses have higher placental levels of DNA methyltransferase 1 (DNMT1) involved in maintenance methylation and respond to maternal variable stress with further increases, supporting the likelihood of continued recreation of methylation patterns [35]. Additionally, prenatal stress impacts de novo methylation patterns only in the brains of male offspring, resulting in changes of methylation status of the corticotropin-releasing factor (*Crf*) promoter and glucocorticoid receptor promoter in the hypothalamus [35] that contribute to lifelong changes in stress hormone signaling.

The epigenetic impact of prenatal stress on offspring is not limited to stressors that affect the mother, and stressors do not have to occur during gestation. Rodent studies in which either female or male parents were stressed during the peripubertal window, before conception, implicate germ cell epigenetic transmission of the stress phenotype from one generation to the next [45]. Stress effects on gene expression through DNA methylation, histone modifications, and noncoding RNAs impact cell-specific gene expression that can lead to alterations in normal cellular functions in the parent as well as offspring. Preclinical studies in male animals found that stress and/or exposure to drugs of abuse produce lasting epigenetic changes in sperm [46,47] that affect the offspring behavior (Table 1) [46–49].

In humans, maternal exposure to famine before conceiving was associated with worse mental health and quality of life for adult offspring, though sex of the offspring was not considered [50]. Studies of children and grandchildren of Holocaust survivors have demonstrated clear adverse effects on the mental health of the first filial generation, but the adverse impact of the Holocaust on mental health of grandchildren appears less

Figure 1. Relationship between stress effects on behavior across the life span and psychiatric disease. For each epoch of the life span, the associated emerging diseases are listed next to the proximal and distal effects of stress exposure at that time point and known changes in brain subregions. 5HT, 5-hydroxytryptamine (serotonin); ACC, anterior cingulate cortex; CORT, corticosterone; CRF, corticotropin-releasing factor; DG, dentate gyrus; DLPFC, dorsal lateral prefrontal cortex; DNMT3a, DNA methyltransferase 3a; ERα, estrogen receptor alpha; F, female; GABA, gamma-aminobutyric acid; GR, glucocorticoid receptor; H, human; HPA, hypothalamic-pituitary-adrenal; LH, lateral habenula; LTP, long-term potentiation; M, male; M1, motor cortex 1; MDD, major depressive disorder; mRNA, messenger RNA; NAc, nucleus accumbens; NMDA, *N*-methyl-D-aspartate; OTX, orthodenticle homeobox; PAG, periaqueductal gray; POA, preoptic area; R, rodent; vmPFC, ventral medial prefrontal cortex; VTA, ventral tegmental area.

Table 1. Sex Differences in Effects of Stress on Hypothalamic-Pituitary-Adrenal Axis Regulation and Behavior in Male and Female Preclinical Studies Across the Life Span

Epoch of Stress Exposure	Male Subjects	Female Subjects
Preconception: Distal	Increased anxiety/depression-associated behaviors Increased response to subsequent stress M > F (46,48,49)	Increased anxiety/depression-associated behaviors Increased response to subsequent stress M > F (46,48,49)
Prenatal Stress: Distal	Increased CORT in response to restraint (38) Decreased sociability and decreased paired plus inhibition (30–33)	Increased CORT, ACTH, and corticosteroid-binding globulin in response to restraint (38)
PPD 1–7	Feminized patterns of spatial navigation in Barnes maze/increased immobility in FST (35) Passive coping/anhedonia (34,35) Decreased spatial learning (37)	
PPD 11 to birth	Increased sensitivity to reward/increased conditioned place preference for chocolate/cocaine (40) Alterations in circadian rhythm and REM sleep includes increased paradoxical/fragmented sleep and decreased slow wave sleep (145)	Passive coping (FST) M < F Decreased sensitivity to reward/decreased conditioned place preference for chocolate/cocaine (40)
Birth-Peripuberty		
Proximal	Increased CORT Decreased growth (62–65)	Increased CORT Decreased growth (62–65)
Distal	Anhedonia Decreased play/decreased social behavior (66–68) Decreased social interaction (146) Cognitive impairments (63,69) Increased susceptibility to adult social defeat (76)	Decreased weight (16) Decreased exploratory anxiety-like behavior/decreased contextual fear conditioning (147) Decreased maternal care (148) Decreased social interaction (146) Blunted HPA activity in response to acute stress pregnancy and pup separation/distress (78,79)
Puberty		
Proximal	Increased period for CORT to return to baseline following acute stress (99,100) Altered weight gain (102,103)	Increased period for CORT to return to baseline following acute stress during puberty (99,100) Blunted CORT response to restraint stress following exposure to chronic stressors (both proximal and distal) (101) Decreased maternalization of virgin females to pups (79) Anhedonia passive coping (101)
Distal	Increased submissive response to conditioned defeat (Syrian hamsters) (115)	Increased submissive response to conditioned defeat (Syrian hamsters) (115)
Adult: Proximal	21-day variable stress: Decreased grooming following 6-day variable stress (splash test), increased latency to eat (NSF), increased immobility (FST) (111,112) Increased ability to learn trace eyeblink conditioning (135)	6-day variable stress: Decreased grooming (splash test), increased latency to eat (NSF), increased immobility (FST), decreased sucrose preference (111) 21-day variable stress: Decreased grooming (splash test), increased latency to eat (NSF), increased immobility (FST), decreased sucrose preference (111,112) Conditioned defeat Decreased ability to learn trace eyeblink conditioning (135)
Senescence: Proximal	No effect of stress on trace eyeblink conditioning (136)	No effect of stress on trace eyeblink conditioning (136) Decreased spatial learning (radial arm maze) (65)

ACTH, adrenocorticotropic hormone; CORT, corticosterone; F, female; FST, forced swim test; HPA, hypothalamic-pituitary-adrenal; M, male; NSF, novelty suppressed feeding; PPD, prepartum day; REM, rapid eye movement.

pronounced (51–53). The adverse effects of childhood and preconception trauma exposures on parental mental health and parenting practices mediate, in part, the effects of parental trauma on offspring mental health; however, recent data also implicate epigenetic mechanisms. Most notably, a study on the offspring of Holocaust survivors identified altered methylation status of the gene encoding FK506 binding protein, a regulator of glucocorticoid receptor sensitivity, in blood (54). These same offspring self-reported depression and anxiety symptoms. Furthermore, exposure of prepubertal girls to the Holocaust effected transmission of risk phenotype to the offspring. Reduction in activity of the enzyme 11β-hydroxysteroid dehydrogenase type 2, which inactivates cortisol, has been noted in Holocaust survivors, though an opposite effect was noted for their offspring. Emphasizing the importance of timing of adversity, the impact of having a mother who experienced the Holocaust was more pronounced with respect to offspring 11β-hydroxysteroid dehydrogenase type 2 activity if the mother was prepubertal at the time and her subsequent offspring was male (55).

STRESS ACROSS THE LIFE SPAN: PROXIMAL AND DISTAL RAMIFICATIONS

Early Life Stress

Studies of children isolated in orphanages in accordance with former policies of the Romanian government have provided insight into the lasting damage of neglect and early life stress even when basic needs such as food and shelter are met. Caregiver deprivation is associated with an accentuation of the female bias toward anxiety and depressive disorders and the male bias toward impulsivity and conduct disorders (56,57). Neuroimaging studies show abnormalities in amygdala development and subsequent response to stimuli, influencing connections to brain regions critical to the evaluation and appropriate response to rewarding and aversive stimuli, in adults (58). Whether imaging outcomes vary by sex is not known, as most studies do not examine data separately for male and female offspring who have suffered severe caregiver deprivation.

In humans, another form of early life stress, high maternal allostatic load, measured by maternal psychological distress and parenting stress was associated with increased risk for socioemotional problems in a prospective, longitudinal study of 1-year-old offspring (59). Offspring hair cortisol levels showed a complex relationship with maternal factors, with offspring levels positively correlated with parent stress but negatively correlated with maternal depression scores (59). In humans, significant adversity before 18 years of age is associated with a host of adverse psychiatric and medical health outcomes regardless of sex (60,61).

In rodents, early life stress that disrupts maternal care (62–65) has proximal effects (Table 1), including increased HPA activity in a traditionally refractory period. Distally in female rodents, there is reduced functional connectivity within cortical areas to brain regions implicated in maternal care, pain modulation, and emotion along with sex differences in behavior (Table 1) (63,66–69). Male rodents, but not female rodents, have cognitive deficits that become more pronounced as they age (70). Decreased ability to perform cognitive tasks in these male rodents was associated with changes in excitability in subregions in the hippocampus that were unmasked only at an advanced age (70). CRF was also increased, and the later cognitive effects were blocked by administration of a CRF antagonist immediately after the period of early life stress exposure (71).

In humans, studies of older adults reflect these preclinical findings. Significant childhood adversity is associated with worse cognitive aging and more rapid declines in processing speed, particularly when there are current depressive symptoms (72). However, the sex differences reported in the preclinical literature may not be relevant to human aging. Childhood adversity accentuates the effects of later-life caregiving stress on inflammation and telomere length, a marker of cellular aging (73), and older women are more likely to be caregivers than men. Women are also at roughly twice the risk of Alzheimer's disease (AD) than men (74). Severity of childhood trauma was associated with greater risk for a dementia diagnosis and AD, although sex differences were not investigated (75).

Prepubescent-Peripubescent Stress

The timing of early life stress with respect to offspring development may also contribute to lasting effects. Preclinical work in male mice demonstrated that late postnatal stress (PND 10–20) produced distal effects on adult responses to social stress (76). The authors discovered that a transcription factor, orthodenticle homeobox 2, contributed by mediating hedonic programming in the ventral tegmental area. A subsequent study in children (8–15 years of age) who experienced maltreatment found that the methylation status of peripheral orthodenticle homeobox 2 predicted depression and was associated with increased functional connectivity between key brain structures associated with mood disorders (77).

Early life stress alters the relationship between HPA axis activation and pregnancy or postpartum stress (Table 1) (78,79). Similarly, psychologically healthy women who self-reported exposure to two or more types of adversities during childhood or adolescence (age 0–18 years) using the Adverse Childhood Experiences Questionnaire also showed a blunted HPA response to separation from their 6-month-old infants (78). It is unclear whether the blunted maternal cortisol response to stress is a sign of risk or resilience. In that individuals who experience significant childhood adversity are more likely to experience significant psychosocial stress later in life (80), a degree of HPA axis blunting may be preferable.

Women who report experiencing two or more types of postpubertal childhood adversities are also more likely to experience a first onset of major depressive disorder during the perimenopause transition compared with women who reported no childhood adversities. Experience of one type of adversity during the prepubertal window was associated with resilience to depression even if the individual went on to experience additional childhood adversities during the postpubertal period (81). Some women are resilient to depression despite exposures to significant early life stress until they experience perimenopause, suggesting an important interaction between gonadal steroids, early life stress, and brain changes during aging. Nonhuman primate studies of social subordinant stress (82) and more recent neuroimaging studies in postmenopausal women (83) suggest that early life stress is associated with enduring estradiol-driven changes in serotonergic functioning and may underlie a risk for depression or cognitive decline during periods of hypogonadism in female subjects (84). Whether this same relationship holds true for older male subjects is not known, but it is important to consider that men do not typically undergo a dramatic change in gonadal steroids with aging. Men who experience natural or iatrogenically induced hypogonadism are also at greater risk for cognitive declines and depression, although the impact of childhood adversity on their risk for depression during hypogonadism is not known (85,86).

Stress During Puberty and Early Adulthood

The adolescent period is a risk factor in the occurrence of many psychiatric disorders in both sexes (87). By age 14 years, 50% of the people who will experience mental illness have had their first occurrence, and this figure increases to 75% by age 24 (88). In girls, early onset of menstruation (before 11.5 years

of age) increases circulating levels of estrogens during adolescence and increases the risk of depression (89). Whereas the developmental changes of adolescence are usually associated with activational effects of gonadal hormones bringing on secondary sexual characteristics, there is growing evidence from the basic and clinical literature recognizing that genetic sex (90,91), organizational effects of gonadal hormones (92–94), and epigenetic mechanisms (95–97) contribute to the development of brain, body, and behavior during this critical period.

Elegant studies have delineated the contribution of the genetic sex complement on gene expression in the frontal cortex of the four core genotypes model following chronic stress in early adulthood (90). This mouse model allows for the dissociation of gonadal sex from genetic sex through manipulation of location of the SRY gene. Having an XY chromosome regardless of gonadal sex reduced gene expression for pathway members of gamma-aminobutyric acid, serotonin, and dopamine signaling in the frontal cortex (90). XY mice in the absence of testosterone expressed increased anxiety-associated behavior compared with XX mice. Testosterone administration was anxiolytic, indicating that the higher levels found in male animals promote resilience by compensating for an underlying vulnerability. Additional studies found a similar pattern in the relationship of somatostatin expression to anxiety-associated behavior in chronically stressed male subjects in the basal lateral amygdala (91). Future work should examine distal effects of stress within this model along with earlier life stress exposure.

Preclinical research indicated that there are proximal neuroendocrine changes in stress reactivity and sex differences in behavior (Table 1) as an individual moves from the prepubertal state to early adulthood (98–103). The effects of stress during puberty are long-lasting and have implications for the development of posttraumatic stress disorder (PTSD) and other stress-based mood disorders in humans (104). During adolescence, girls are three times more likely to develop PTSD than boys (105). Sex or gender differences in cognitive styles contribute to resilience for PTSD and other mood disorders. Girls who experienced either early life or adolescent abuse are more likely to use internalizing coping strategies predictive for increased risk for PTSD (106). Traumatized girls entering puberty (age 8–13 years) are more likely to engage in self-blame and avoidance, whereas traumatized boys tend to report intrusive or reexperiencing symptoms (107). When nontraumatized children were exposed to fear conditioning in an experimental setting, girls, but not boys, showed generalized fear and lack of ability to discriminate a safety signal.

Gonadal steroid fluctuations across the menstrual cycle are also thought to contribute directly to risk and symptoms of PTSD (108). Among women with PTSD, phobic anxiety is increased during the follicular phase when estradiol levels are low. This finding was not observed in traumatized women without PTSD and nontrauma control subjects (109). In healthy women, low estradiol levels are also associated with stronger intrusive memories in an experimental paradigm (110). Taken together, these data support that timing of traumatic exposures with respect to menstrual cycle phase and thus natural gonadal steroid levels may contribute to risk or resilience for subsequent PTSD. Moreover, behavioral treatments for PTSD

may be more successful if menstrual cycle phases and use of steroid contraceptives are considered.

Gonadal hormones also contribute directly to the effects of stress on behavior in animals. Female mice, but not male mice, respond to 6 days of variable stress, whereas both sexes respond to 21 days of stress (Table 1) (111,112). These sex differences involve increased signaling between the lateral habenula and the ventral tegmental area that occurs only in female subjects (113). Ovariectomy blocks the behavioral responses to 6 days of stress (114); it is not known whether gonadectomy also blocks the effects of longer periods of variable stress in female animals or whether male resilience is dependent on gonadal hormones. The existing literature suggests that resilience for other stress models may be regulated via gonadal hormones (115). In male animals, submissive behavior following conditioned defeat was dependent on testosterone. Castrated male animals express more submissive behavior following fewer attacks. Testosterone or dihydrotestosterone replacement reduced submissive behavior in castrated male animals (116). Studies of social stress in young adult mice also indicate a neuromodulatory role for hormones, as estrogen receptor alpha (ERα) expression was functionally linked to resilience. Male mice that were susceptible to social defeat stress had decreased ERα expression in the nucleus accumbens, and increasing expression of ERα promoted resilience (117). Nuclear ERα expression was also decreased in nucleus accumbens of male and female mice that underwent variable stress, and overexpression promoted resilience in both sexes (117). Different transcriptional targets were regulated in male and female animals following overexpression of ERα, indicating that different downstream molecular mechanisms regulate resilience in male and female animals. Molecular sex differences in response to stress have been replicated in other species, including Syrian hamsters (118), and are seen in postmortem tissue taken from humans with a diagnosis of major depressive disorder (112).

DNMT3a is a de novo methyltransferase that regulates sex differences in the adult transcriptome (111). Masculinizing female transcriptional signatures by reducing levels of DNMT3a blocked the effects of variable stress in female subjects. Gene ontogeny identified the CRF pathway shifting most toward a male transcriptional pattern. Viral mediated overexpression of DNMT3a made male and female subjects responsive to subthreshold variable stress and microdefeat (111,119). Postmortem nucleus accumbens tissue from men and women with major depressive disorder had increased DNMT3a expression, and a history of antidepressant treatment at time of death partially attenuated the increase (111). In male mice that were behaviorally susceptible to social defeat, stress infusion of a DNA methylation inhibitor reversed social avoidance behavior similar to the effects of 28 days of systemic treatment with fluoxetine (119).

Some of the individual differences in CRF signaling in response to adult stress are due to epigenetic regulation of the Crf promoter. Stress-susceptible male mice have higher levels of CRF expression in the hypothalamus than resilient animals owing to decreased methylation of the Crf promoter (120). Antidepressant treatment blocks Crf promoter methylation and social anhedonia, whereas infusion into the

hypothalamus of small interfering RNA sequences targeted to *Crf* promoted resilience. There is growing evidence of sex differences in CRF activation in response to stress in adulthood (121). Stress-induced activation of CRF negatively affects attention and cognitive function in men, but not women. Men are more sensitive to cholinergic CRF activation, whereas women respond with a noradrenergic mediated hyperarousal and vigilant state (122). These effects likely arise from region-specific sex differences in the CRF1 receptor internalization (123,124).

Stress During Senescence

Menopause and andropause are another period of changing hormones during which there are increased risks for emergence of psychiatric and cognitive issues. About 20% of women experience a debilitating menopause characterized by depression, cognitive changes, sleep difficulties, and moderate to severe vasomotor symptoms (125). Perimenopausal women are at increased risk of affective and cognitive complaints, although the risk for new onset and recurrence of major depression declines in the years following the final menstrual period (126). Premature menopause, defined as final menstrual period before the age of 40, is associated with even greater risk for affective and cognitive disturbances. The fact that men typically experience later onset and a more protracted decline in testosterone production may contribute to their resilience to adverse cognitive and mood changes with aging. When andropause occurs prematurely, men too experience adverse effects on health and quality of life (127).

Menopause leads to changes in the HPA axis (128) that may enhance the adverse effects of stress. Postmenopausal women not using estradiol therapy (ET) tend to have greater cortisol response to acute stress than age-matched men and younger adults (129), and increasing levels of urinary cortisol over time have been associated with worse baseline memory recall and increased memory decline over a 2-year period (130). The impact of ET on HPA axis response to stress in postmenopausal women is inconsistent and may be influenced by timing of administration onset with respect to the final menstrual period, dose of ET, and duration of use. Short-term estradiol administration in women who have been hypogonadal for many years appears to adversely sensitize cognitive and behavioral response to stress, whereas the opposite occurs in premenopausal women (131,132). Longer-term use of ET in postmenopausal women appears to blunt cortisol response to stress and reduce the negative effects of stress on working memory (133). Among individuals 54 to 72 years of age who were not given hormone replacement, only women showed a negative impact of a stressor on verbal memory. Women in this age group are likely to be postmenopausal, and again cortisol levels were associated with worse performance in women only (134).

Although preclinical studies on the effects of stress on cognition in aging mice are very limited, they imply that acute and chronic stress have different impacts on cognitive function in aged animals compared with young animals (Table 1) (135,136), and these effects are in part mediated by sex-specific *N*-methyl-D-aspartate receptor–dependent changes in CA1 spine density (137). Acute stress also decreased cell proliferation in the hippocampus of female mice, but not aged male mice, in the absence of effects on spatial learning and could be ameliorated by group housing (138). Additional studies demonstrate drastically reduced levels of neurogenesis in the hippocampus of female mice as they age and behavioral effects (Table 1) (65). These aged female mice had different regulation of insulin and melanocortin-4 receptors in the hypothalamus compared with young stressed female mice. Based on the clinical literature, there is a genuine unmet need to examine the mechanisms through which hormones interact with stress in
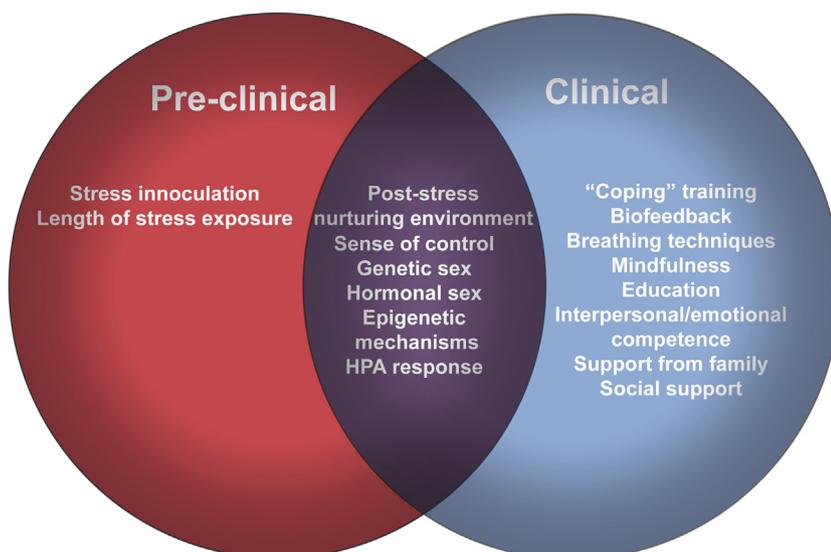

Figure 2. Methods and mechanisms of promoting resilience. Venn diagrams display methods of promoting resilience in animal models (red) and human subjects (blue) and methods/mechanisms that translate across species (purple). HPA, hypothalamic-pituitary-adrenal.

both sexes to promote cognitive and emotional resilience as an individual ages.

It was originally proposed that depression during the life span was a risk factor for developing AD. A meta-analysis showed a significant positive correlation between the length of time a person had a diagonsis of depression and his or her risk of getting AD, suggesting that depression was not a prodrome of dementia (139). However, recent longitudinal studies found that people with earlier onset of depression are not at greater risk of AD, even if they experienced episodes later in life (139,140). Instead, our current understanding is that late-onset depression is indeed a prodrome of dementia. Individuals with a first episode of depression after the age of 50 are at 46% greater risk of all-cause dementia, and significant depressive symptoms at age 65 or older were associated with a 71% greater risk of dementia. Retrospective analysis of data over 28 years showed that differences in depression symptoms were apparent 11 years before the diagnosis of dementia, with an accelerated increase in depressive symptoms occurring in the decade before dementia diagnosis (140). Similarly, increasing, but not steady or declining, depressive symptoms over a 10-year period in older individuals were associated with increased risk for all-cause dementia and AD (141). Similar to depression, AD is more common in women than in men (142,143). Most studies examining the relationship between depression symptoms and risk for dementia control for sex in their analyses and do not report findings for men and women separately. The Baltimore Longitudinal Study of Aging, the one study to do so, reported that the relationship between depression symptoms and all dementia, including AD, was significant for men, but not women (144).

CONCLUSIONS

Male offspring are at greater risk of adverse proximal and some distal behavioral effects of gestational and early life stress owing to a lack of compensatory mechanisms and alterations in epigenetic regulation and organizational effects of hormones. The greatest distal impact of stress in male offspring at all life span epochs seems to be on cognitive ability, particularly spatial learning, and may contribute symptoms associated with autism spectrum disorder, attention-deficit/hyperactivity disorder, and the relationship between depression and AD later in life. Whereas female offspring demonstrate compensatory mechanisms that protect them from the effects of early life stress on cognition, the impact is still present when emotion-related behavior is measured later in life, and the effects are unmasked during periods of dynamic hormonal changes, including puberty, pregnancy, and menopause. In general, periods of fluctuating hormones appear to be a greater risk factor for both the proximal and the distal effects of stress in women.

The impact of sex on risk and resilience to stress is complex and varies according to characteristics of the stressor, such as type, timing, and duration, as well as development with its associated changes in brain structure and function and central and peripheral levels of gonadal steroids. Similarly, the negative effects of stress can be observed immediately in both animal models and humans or can endure for years without apparent health effects until many years later. In fact, effects of childhood adversity on mood and cognition may require specific hormonal and/or developmental states, such as those that occur at menopause and with aging, in order to be revealed. Epigenetic regulation of hormonal state and genetic sex differences are driving factors affecting stress susceptibility and resilience in animal models and are implicated in complex human disease states. As preclinical and clinical research works toward personalized treatments, we will need to start considering that mechanisms contributing to disease state may differ by sex and by age. As researchers, we need to start examining corresponding end points in clinical and preclinical studies. Only then will we be able to understand how mechanisms of resilience (Figure 2) protect individuals from specific symptoms across diseases.

ARTICLE INFORMATION

From the School of Neuroscience (GEH), Virginia Polytechnic Institute and State University, Blacksburg, Virginia; and Department of Psychiatry (CNE), University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, Colorado.

Address correspondence to Georgia E. Hodes, Ph.D., Virginia Polytechnic Institute and State University, School of Neuroscience, 1981 Kraft Drive, Blacksburg, VA 24060; E-mail: ghodes@vt.edu.

Received Jan 3, 2019; revised Apr 8, 2019; accepted Apr 25, 2019.

REFERENCES

1. Menard C, Pfau ML, Hodes GE, Russo SJ (2017): Immune and neuroendocrine mechanisms of stress vulnerability and resilience. Neuropsychopharmacology 42:62–80.
2. McEwen BS (2002): Sex, stress and the hippocampus: Allostasis, allostatic load and the aging process. Neurobiol Aging 23:921–939.
3. Russo SJ, Murrough JW, Han MH, Charney DS, Nestler EJ (2012): Neurobiology of resilience. Nat Neurosci 15:1475–1484.
4. Brockhurst J, Cheleuitte-Nieves C, Buckmaster CL, Schatzberg AF, Lyons DM (2015): Stress inoculation modeled in mice. Transl Psychiatry 5:e537.
5. Hourani L, Tueller S, Kizakevich P, Lewis G, Strange L, Weimer B, et al. (2016): Toward preventing post-traumatic stress disorder: Development and testing of a pilot predeployment stress inoculation training program. Mil Med 181:1151–1160.
6. Morrison KE, Narasimhan S, Fein E, Bale TL (2016): Peripubertal stress with social support promotes resilience in the face of aging. Endocrinology 157:2002–2014.
7. Gillman L, Adams J, Kovac R, Kilcullen A, House A, Doyle C (2015): Strategies to promote coping and resilience in oncology and palliative care nurses caring for adult patients with malignancy: A comprehensive systematic review. JBI Database System Rev Implement Rep 13:131–204.
8. Domhardt M, Munzer A, Fegert JM, Goldbeck L (2015): Resilience in survivors of child sexual abuse: A systematic review of the literature. Trauma Violence Abuse 16:476–493.

9. Jackson A, Cavanagh J, Scott J (2003): A systematic review of manic and depressive prodromes. J Affect Disord 74:209–217.

10. Savill M, D'Ambrosio J, Cannon TD, Loewy RL (2018): Psychosis risk screening in different populations using the Prodromal Questionnaire: A systematic review. Early Interv Psychiatry 12:3–14.

11. Secinti E, Thompson EJ, Richards M, Gaysina D (2017): Research review: Childhood chronic physical illness and adult emotional health—a systematic review and meta-analysis. J Child Psychol Psychiatry 58:753–769.

12. Zucker I, Beery AK (2010): Males still dominate animal studies. Nature 465:690.

13. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB (1993): Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. J Affect Disord 29:8–96.

14. Kessler RC (2003): Epidemiology of women and depression. J Affect Disord 74:5–13.

15. Brown AS, Susser ES, Lin SP, Neugebauer R, Gorman JM (1995): Increased risk of affective disorders in males after second trimester prenatal exposure to the Dutch hunger winter of 1944-45. Br J Psychiatry 166:601–606.

16. Franzek EJ, Sprangers N, Janssens AC, Van Duijn CM, Van De Wetering BJ (2008): Prenatal exposure to the 1944-45 Dutch 'hunger winter' and addiction later in life. Addiction 103:433–438.

17. Hoek HW, Brown AS, Susser E (1998): The Dutch famine and schizophrenia spectrum disorders. Soc Psychiatry Psychiatr Epidemiol 33:373–379.

18. St Clair D, Xu M, Wang P, Yu Y, Fang Y, Zhang F, et al. (2005): Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959-1961. JAMA 294:557–562.

19. Dantzer R (2004): Cytokine-induced sickness behaviour: A neuro-immune response to activation of innate immunity. Eur J Pharmacol 500:399–411.

20. Hart BL (1988): Biological basis of the behavior of sick animals. Neurosci Biobehav Rev 12:123–137.

21. Clifton VL, Murphy VE (2004): Maternal asthma as a model for examining fetal sex-specific effects on maternal physiology and placental mechanisms that regulate human fetal growth. Placenta 25(Suppl A):S45–S52.

22. Clifton VL (2010): Review: Sex and the human placenta: Mediating differential strategies of fetal growth and survival. Placenta 31(Suppl):S33–S39.

23. Murphy VE, Gibson PG, Giles WB, Zakar T, Smith R, Bisits AM, et al. (2003): Maternal asthma is associated with reduced female fetal growth. Am J Respir Crit Care Med 168:1317–1323.

24. Murphy VE, Smith R, Giles WB, Clifton VL (2006): Endocrine regulation of human fetal growth: The role of the mother, placenta, and fetus. Endocr Rev 27:141–169.

25. Torche F, Kleinhaus K (2012): Prenatal stress, gestational age and secondary sex ratio: The sex-specific effects of exposure to a natural disaster in early pregnancy. Hum Reprod 27:558–567.

26. Brown AS (2012): Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. Dev Neurobiol 72:1272–1276.

27. Khashan AS, Abel KM, McNamee R, Pedersen MG, Webb RT, Baker PN, et al. (2008): Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. Arch Gen Psychiatry 65:146–152.

28. Kinney DK, Miller AM, Crowley DJ, Huang E, Gerber E (2008): Autism prevalence following prenatal exposure to hurricanes and tropical storms in Louisiana. J Autism Dev Disord 38:481–488.

29. Ronald A, Pennell CE, Whitehouse AJ (2010): Prenatal maternal stress associated with ADHD and autistic traits in early childhood. Front Psychol 1:223.

30. Jouda J, Wohr M, Del Rey A (2019): Immunity and ultrasonic vocalization in rodents. Ann N Y Acad Sci 1437:68–82.

31. Malkova NV, Yu CZ, Hsiao EY, Moore MJ, Patterson PH (2012): Maternal immune activation yields offspring displaying mouse versions of the three core symptoms of autism. Brain Behav Immun 26:607–616.

32. Shi L, Fatemi SH, Sidwell RW, Patterson PH (2003): Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. J Neurosci 23:297–302.

33. Holloway T, Moreno JL, Umali A, Rayannavar V, Hodes GE, Russo SJ, et al. (2013): Prenatal stress induces schizophrenia-like alterations of serotonin 2A and metabotropic glutamate 2 receptors in the adult offspring: Role of maternal immune system. J Neurosci 33:1088–1098.

34. Goel N, Bale TL (2009): Examining the intersection of sex and stress in modelling neuropsychiatric disorders. J Neuroendocrinol 21:415–420.

35. Mueller BR, Bale TL (2008): Sex-specific programming of offspring emotionality after stress early in pregnancy. J Neurosci 28:9055–9065.

36. Mueller BR, Bale TL (2007): Early prenatal stress impact on coping strategies and learning performance is sex dependent. Physiol Behav 91:55–65.

37. Weinstock M (2008): The long-term behavioural consequences of prenatal stress. Neurosci Biobehav Rev 32:1073–1086.

38. McCormick CM, Smythe JW, Sharma S, Meaney MJ (1995): Sex-specific effects of prenatal stress on hypothalamic-pituitary-adrenal responses to stress and brain glucocorticoid receptor density in adult rats. Brain Res Dev Brain Res 84:55–61.

39. Alonso SJ, Arevalo R, Afonso D, Rodriguez M (1991): Effects of maternal stress during pregnancy on forced swimming test behavior of the offspring. Physiol Behav 50:511–517.

40. Reynaert ML, Marrocco J, Mairesse J, Lionetto L, Simmaco M, Deruyter L, et al. (2016): Hedonic sensitivity to natural rewards is affected by prenatal stress in a sex-dependent manner. Addict Biol 21:1072–1085.

41. Samuelsson AM, Jennische E, Hansson HA, Holmang A (2006): Prenatal exposure to interleukin-6 results in inflammatory neuro-degeneration in hippocampus with NMDA/GABA(A) dysregulation and impaired spatial learning. Am J Physiol Regul Integr Comp Physiol 290:R1345–R1356.

42. Semple BD, Blomgren K, Gimlin K, Ferriero DM, Noble-Haeusslein LJ (2013): Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. Prog Neurobiol 106–107:1–16.

43. Nugent BM, Wright CL, Shetty AC, Hodes GE, Lenz KM, Mahurkar A, et al. (2015): Brain feminization requires active repression of masculinization via DNA methylation. Nat Neurosci 18:690–697.

44. Bogdanovic O, Veenstra GJ (2009): DNA methylation and methyl-CpG binding proteins: Developmental requirements and function. Chromosoma 118:549–565.

45. Chan JC, Nugent BM, Bale TL (2018): Parental advisory: Maternal and paternal stress can impact offspring neurodevelopment. Biol Psychiatry 83:886–894.

46. Rodgers AB, Morgan CP, Leu NA, Bale TL (2015): Transgenerational epigenetic programming via sperm microRNA recapitulates effects of paternal stress. Proc Natl Acad Sci U S A 112:13699–13704.

47. Vassoler FM, White SL, Schmidt HD, Sadri-Vakili G, Pierce RC (2013): Epigenetic inheritance of a cocaine-resistance phenotype. Nat Neurosci 16:42–47.

48. White SL, Vassoler FM, Schmidt HD, Pierce RC, Wimmer ME (2016): Enhanced anxiety in the male offspring of sires that self-administered cocaine. Addict Biol 21:802–810.

49. Dietz DM, Laplant Q, Watts EL, Hodes GE, Russo SJ, Feng J, et al. (2011): Paternal transmission of stress-induced pathologies. Biol Psychiatry 70:408–414.

50. Stein AD, Pierik FH, Verrips GH, Susser ES, Lumey LH (2009): Maternal exposure to the Dutch famine before conception and during pregnancy: Quality of life and depressive symptoms in adult offspring. Epidemiology 20:909–915.

51. Sagi-Schwartz A, van IMH, Bakermans-Kranenburg MJ (2008): Does intergenerational transmission of trauma skip a generation? No meta-analytic evidence for tertiary traumatization with third generation of Holocaust survivors. Attach Hum Dev 10:105–121.

52. Kassai SC, Motta RW (2006): An investigation of potential Holocaust-related secondary traumatization in the third generation. Int J Emerg Ment Health 8:35–47.

53. Zerach G, Solomon Z (2016): Low levels of posttraumatic stress symptoms and psychiatric symptomatology among third-generation Holocaust survivors whose fathers were war veterans. J Psychiatr Res 73:25–33.

54. Yehuda R, Daskalakis NP, Bierer LM, Bader HN, Klengel T, Holsboer F, et al. (2016): Holocaust exposure induced intergenerational effects on FKBP5 methylation. Biol Psychiatry 80:372–380.

55. Bierer LM, Bader HN, Daskalakis NP, Lehrner AL, Makotkine I, Seckl JR, et al. (2014): Elevation of 11beta-hydroxysteroid dehydrogenase type 2 activity in Holocaust survivor offspring: Evidence for an intergenerational effect of maternal trauma exposure. Psychoneuroendocrinology 48:1–10.

56. Ellis BH, Fisher PA, Zaharie S (2004): Predictors of disruptive behavior, developmental delays, anxiety, and affective symptomatology among institutionally reared romanian children. J Am Acad Child Adolesc Psychiatry 43:1283–1292.

57. Zeanah CH, Egger HL, Smyke AT, Nelson CA, Fox NA, Marshall PJ, et al. (2009): Institutional rearing and psychiatric disorders in Romanian preschool children. Am J Psychiatry 166:777–785.

58. Fareri DS, Tottenham N (2016): Effects of early life stress on amygdala and striatal development. Dev Cogn Neurosci 19:233–247.

59. Palmer FB, Anand KJ, Graff JC, Murphy LE, Qu Y, Volgyi E, et al. (2013): Early adversity, socioemotional development, and stress in urban 1-year-old children. J Pediatr 163:1733–1739.e1731.

60. Van Niel C, Pachter LM, Wade R Jr, Felitti VJ, Stein MT (2014): Adverse events in children: predictors of adult physical and mental conditions. J Dev Behav Pediatr 35:549–551.

61. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. (1998): Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 14:245–258.

62. Nephew BC, Bridges RS (2011): Effects of chronic social stress during lactation on maternal behavior and growth in rats. Stress 14:677–684.

63. Rice CJ, Sandman CA, Lenjavi MR, Baram TZ (2008): A novel mouse model for acute and long-lasting consequences of early life stress. Endocrinology 149:4892–4900.

64. Bolton JL, Molet J, Ivy A, Baram TZ (2017): New insights into early-life stress and behavioral outcomes. Curr Opin Behav Sci 14:133–139.

65. Lotan A, Lifschytz T, Wolf G, Keller S, Ben-Ari H, Tatarsky P, et al. (2018): Differential effects of chronic stress in young-adult and old female mice: Cognitive-behavioral manifestations and neurobiological correlates. Mol Psychiatry 23:1432–1445.

66. Bolton JL, Molet J, Regev L, Chen Y, Rismanchi N, Haddad E, et al. (2018): Anhedonia following early-life adversity involves aberrant interaction of reward and anxiety circuits and is reversed by partial silencing of amygdala corticotropin-releasing hormone gene. Biol Psychiatry 83:137–147.

67. Molet J, Heins K, Zhuo X, Mei YT, Regev L, Baram TZ, et al. (2016): Fragmentation and high entropy of neonatal experience predict adolescent emotional outcome. Transl Psychiatry 6:e702.

68. Bolton JL, Ruiz CM, Rismanchi N, Sanchez GA, Castillo E, Huang J, et al. (2018): Early-life adversity facilitates acquisition of cocaine self-administration and induces persistent anhedonia. Neurobiol Stress 8:57–67.

69. Kanatsou S, Karst H, Kortesidou D, van den Akker RA, den Blaauwen J, Harris AP, et al. (2017): Overexpression of mineralocorticoid receptors in the mouse forebrain partly alleviates the effects of chronic early life stress on spatial memory, neurogenesis and synaptic function in the dentate gyrus. Front Cell Neurosci 11:132.

70. Brunson KL, Kramar E, Lin B, Chen Y, Colgin LL, Yanagihara TK, et al. (2005): Mechanisms of late-onset cognitive decline after early-life stress. J Neurosci 25:9328–9338.

71. Ivy AS, Rex CS, Chen Y, Dube C, Maras PM, Grigoriadis DE, et al. (2010): Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. J Neurosci 30:13005–13015.

72. Korten NC, Penninx BW, Pot AM, Deeg DJ, Comijs HC (2014): Adverse childhood and recent negative life events: Contrasting associations with cognitive decline in older persons. J Geriatr Psychiatry Neurol 27:128–138.

73. Kiecolt-Glaser JK, Gouin JP, Weng NP, Malarkey WB, Beversdorf DQ, Glaser R (2011): Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. Psychosom Med 73:16–22.

74. Podcasy JL, Epperson CN (2016): Considering sex and gender in Alzheimer disease and other dementias. Dialogues Clin Neurosci 18:437–446.

75. Radford K, Delbaere K, Draper B, Mack HA, Daylight G, Cumming R, et al. (2017): Childhood stress and adversity is associated with late-life dementia in Aboriginal Australians. Am J Geriatr Psychiatry 25:1097–1106.

76. Pena CJ, Kronman HG, Walker DM, Cates HM, Bagot RC, Purushothaman I, et al. (2017): Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2. Science 356:1185–1188.

77. Kaufman J, Wymbs NF, Montalvo-Ortiz JL, Orr C, Albaugh MD, Althoff R, et al. (2018): Methylation in OTX2 and related genes, maltreatment, and depression in children. Neuropsychopharmacology 43:2204–2211.

78. Morrison KE, Epperson CN, Sammel MD, Ewing G, Podcasy JS, Hantsoo L, et al. (2017): Preadolescent adversity programs a disrupted maternal stress reactivity in humans and mice. Biol Psychiatry 81:693–701.

79. Shors TJ, Tobomicronn K, DiFeo G, Durham DM, Chang HY (2016): Sexual Conspecific Aggressive Response (SCAR): A model of sexual trauma that disrupts maternal learning and plasticity in the female brain. Sci Rep 6:18960.

80. Manyema M, Norris SA, Richter LM (2018): Stress begets stress: The association of adverse childhood experiences with psychological distress in the presence of adult life stress. BMC Public Health 18:835.

81. Epperson CN, Sammel MD, Bale TL, Kim DR, Conlin S, Scalice S, et al. (2017): Adverse childhood experiences and risk for first-episode major depression during the menopause transition. J Clin Psychiatry 78:e298–e307.

82. Kaplan JR, Adams MR, Clarkson TB, Manuck SB, Shively CA (1991): Social behavior and gender in biomedical investigations using monkeys: studies in atherogenesis. Lab Anim Sci 41:334–343.

83. Shanmugan S, Loughead J, Cao W, Sammel MD, Satterthwaite TD, Ruparel K, et al. (2017): Impact of tryptophan depletion on executive system function during menopause is moderated by childhood adversity. Neuropsychopharmacology 42:2398–2406.

84. Shanmugan S, Epperson CN (2014): Estrogen and the prefrontal cortex: Towards a new understanding of estrogen's effects on executive functions in the menopause transition. Hum Brain Mapp 35:847–865.

85. Khosravi S, Ardebili HE, Larijani B, Nedjat S, Nikbakht Nasrabadi A, Ardebili ME, et al. (2015): Are andropause symptoms related to depression? Aging Clin Exp Res 27:813–820.

86. Sato Y, Tanda H, Kato S, Onishi S, Nakajima H, Nanbu A, et al. (2007): Prevalence of major depressive disorder in self-referred patients in a late onset hypogonadism clinic. Int J Impot Res 19:407–410.

87. Breslau J, Gilman SE, Stein BD, Ruder T, Gmelin T, Miller E (2017): Sex differences in recent first-onset depression in an epidemiological sample of adolescents. Transl Psychiatry 7:e1139.

88. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005): Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62:593–602.

89. Joinson C, Heron J, Lewis G, Croudace T, Araya R (2011): Timing of menarche and depressive symptoms in adolescent girls from a UK cohort. Br J Psychiatry 198:17–23.

90. Seney ML, Ekong KI, Ding Y, Tseng GC, Sibille E (2013): Sex chromosome complement regulates expression of mood-related genes. Biol Sex Differ 4:20.

91. Puralewski R, Vasilakis G, Seney ML (2016): Sex-related factors influence expression of mood-related genes in the basolateral amygdala differentially depending on age and stress exposure. Biol Sex Differ 7:50.

92. Schulz KM, Sisk CL (2016): The organizing actions of adolescent gonadal steroid hormones on brain and behavioral development. Neurosci Biobehav Rev 70:148–158.

93. De Lorme KC, Sisk CL (2016): The organizational effects of pubertal testosterone on sexual proficiency in adult male Syrian hamsters. Physiol Behav 165:273–277.

94. Schulz KM, Richardson HN, Zehr JL, Osetek AJ, Menard TA, Sisk CL (2004): Gonadal hormones masculinize and defeminize reproductive behaviors during puberty in the male Syrian hamster. Horm Behav 45:242–249.

95. Bessa DS, Maschietto M, Aylwin CF, Canton APM, Brito VN, Macedo DB, et al. (2018): Methylome profiling of healthy and central precocious puberty girls. Clin Epigenetics 10:146.

96. Lomniczi A, Wright H, Castellano JM, Matagne V, Toro CA, Ramaswamy S, et al. (2015): Epigenetic regulation of puberty via Zinc finger protein-mediated transcriptional repression. Nat Commun 6:10195.

97. Lomniczi A, Loche A, Castellano JM, Ronnekleiv OK, Bosch M, Kaidar G, et al. (2013): Epigenetic control of female puberty. Nat Neurosci 16:281–289.

98. Foilb AR, Lui P, Romeo RD (2011): The transformation of hormonal stress responses throughout puberty and adolescence. J Endocrinol 210:391–398.

99. Romeo RD, Karatsoreos IN, McEwen BS (2006): Pubertal maturation and time of day differentially affect behavioral and neuroendocrine responses following an acute stressor. Horm Behav 50:463–468.

100. Romeo RD, Lee SJ, McEwen BS (2004): Differential stress reactivity in intact and ovariectomized prepubertal and adult female rats. Neuroendocrinology 80:387–393.

101. Bourke CH, Neigh GN (2011): Behavioral effects of chronic adolescent stress are sustained and sexually dimorphic. Horm Behav 60:112–120.

102. Kaplowitz ET, Savenkova M, Karatsoreos IN, Romeo RD (2016): Somatic and neuroendocrine changes in response to chronic corticosterone exposure during adolescence in male and female rats. J Neuroendocrinol 28:12336.

103. Weintraub A, Singaravelu J, Bhatnagar S (2010): Enduring and sex-specific effects of adolescent social isolation in rats on adult stress reactivity. Brain Res 1343:83–92.

104. Westfall NC, Nemeroff CB (2015): The preeminence of early life trauma as a risk factor for worsened long-term health outcomes in women. Curr Psychiatry Rep 17:90.

105. McLaughlin KA, Koenen KC, Hill ED, Petukhova M, Sampson NA, Zaslavsky AM, et al. (2013): Trauma exposure and posttraumatic stress disorder in a national sample of adolescents. J Am Acad Child Adolesc Psychiatry 52:815–830.e814.

106. Herringa RJ, Birn RM, Ruttle PL, Burghy CA, Stodola DE, Davidson RJ, et al. (2013): Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. Proc Natl Acad Sci U S A 110:19119–19124.

107. Gamwell K, Nylocks M, Cross D, Bradley B, Norrholm SD, Jovanovic T (2015): Fear conditioned responses and PTSD symptoms in children: Sex differences in fear-related symptoms. Dev Psychobiol 57:799–808.

108. Garcia NM, Walker RS, Zoellner LA (2018): Estrogen, progesterone, and the menstrual cycle: A systematic review of fear learning, intrusive memories, and PTSD. Clin Psychol Rev 66:80–96.

109. Pineles SL, Nillni YI, King MW, Patton SC, Bauer MR, Mostoufi SM, et al. (2016): Extinction retention and the menstrual cycle: Different associations for women with posttraumatic stress disorder. J Abnorm Psychol 125:349–355.

110. Wegerer M, Kerschbaum H, Blechert J, Wilhelm FH (2014): Low levels of estradiol are associated with elevated conditioned responding during fear extinction and with intrusive memories in daily life. Neurobiol Learn Mem 116:145–154.

111. Hodes GE, Pfau ML, Purushothaman I, Ahn HF, Golden SA, Christoffel DJ, et al. (2015): Sex differences in nucleus accumbens transcriptome profiles associated with susceptibility versus resilience to subchronic variable stress. J Neurosci 35:16362–16376.

112. Labonte B, Engmann O, Purushothaman I, Menard C, Wang J, Tan C, et al. (2017): Sex-specific transcriptional signatures in human depression. Nat Med 23:1102–1111.

113. Zhang S, Zhang H, Ku SM, Juarez B, Morel C, Tzavaras N, et al. (2018): Sex differences in the neuroadaptations of reward-related circuits in response to subchronic variable stress. Neuroscience 376:108–116.

114. LaPlant Q, Chakravarty S, Vialou V, Mukherjee S, Koo JW, Kalahasti G, et al. (2009): Role of nuclear factor kappaB in ovarian hormone-mediated stress hypersensitivity in female mice. Biol Psychiatry 65:874–880.

115. Rosenhauer AM, McCann KE, Norvelle A, Huhman KL (2017): An acute social defeat stressor in early puberty increases susceptibility to social defeat in adulthood. Horm Behav 93:31–38.

116. Solomon MB, Karom MC, Norvelle A, Markham CA, Erwin WD, Huhman KL (2009): Gonadal hormones modulate the display of conditioned defeat in male Syrian hamsters. Horm Behav 56:423–428.

117. Lorsch ZS, Loh YE, Purushothaman I, Walker DM, Parise EM, Salery M, et al. (2018): Estrogen receptor alpha drives pro-resilient transcription in mouse models of depression. Nat Commun 9:1116.

118. McCann KE, Sinkiewicz DM, Rosenhauer AM, Beach LQ, Huhman KL (2019): Transcriptomic analysis reveals sex-dependent expression patterns in the basolateral amygdala of dominant and subordinate animals after acute social conflict. Mol Neurobiol 56:3768–3779.

119. LaPlant Q, Vialou V, Covington HE 3rd, Dumitriu D, Feng J, Warren BL, et al. (2010): Dnmt3a regulates emotional behavior and spine plasticity in the nucleus accumbens. Nat Neurosci 13:1137–1143.

120. Elliott E, Ezra-Nevo G, Regev L, Neufeld-Cohen A, Chen A (2010): Resilience to social stress coincides with functional DNA methylation of the Crf gene in adult mice. Nat Neurosci 13:1351–1353.

121. Bangasser DA, Eck SR, Ordones Sanchez E (2019): Sex differences in stress reactivity in arousal and attention systems. Neuropsychopharmacology 44:129–139.

122. Bangasser DA, Eck SR, Telenson AM, Salvatore M (2018): Sex differences in stress regulation of arousal and cognition. Physiol Behav 187:42–50.

123. Bangasser DA, Curtis A, Reyes BA, Bethea TT, Parastatidis I, Ischiropoulos H, et al. (2010): Sex differences in corticotropin-releasing factor receptor signaling and trafficking: Potential role in female vulnerability to stress-related psychopathology. Mol Psychiatry 15:877, 896–904.

124. McAlinn HR, Reich B, Contoreggi NH, Kamakura RP, Dyer AG, McEwen BS, et al. (2018): Sex differences in the subcellular distribution of corticotropin-releasing factor receptor 1 in the rat hippocampus following chronic immobilization stress. Neuroscience 383:98–113.

125. Hu LY, Shen CC, Hung JH, Chen PM, Wen CH, Chiang YY, et al. (2016): Risk of psychiatric disorders following symptomatic menopausal transition: A nationwide population-based retrospective cohort study. Medicine (Baltimore) 95:e2800.

126. Freeman EW, Sammel MD, Boorman DW, Zhang R (2014): Longitudinal pattern of depressive symptoms around natural menopause. JAMA Psychiatry 71:36–43.

127. Saad F, Gooren LJ (2014): Late onset hypogonadism of men is not equivalent to the menopause. Maturitas 79:52–57.

128. Woods NF, Carr MC, Tao EY, Taylor HJ, Mitchell ES (2006): Increased urinary cortisol levels during the menopausal transition. Menopause 13:212–221.

129. Bale TL, Epperson CN (2015): Sex differences and stress across the lifespan. Nat Neurosci 18:1413–1420.

130. Seeman TE, McEwen BS, Singer BH, Albert MS, Rowe JW (1997): Increase in urinary cortisol excretion and memory declines: MacArthur studies of successful aging. J Clin Endocrinol Metab 82:2458–2465.

131. Albert K, Pruessner J, Newhouse P (2015): Estradiol levels modulate brain activity and negative responses to psychosocial stress across the menstrual cycle. Psychoneuroendocrinology 59:14–24.

132. Newhouse PA, Dumas J, Wilkins H, Coderre E, Sites CK, Naylor M, et al. (2010): Estrogen treatment impairs cognitive performance after psychosocial stress and monoamine depletion in postmenopausal women. Menopause 17:860–873.

133. Herrera AY, Hodis HN, Mack WJ, Mather M (2017): Estradiol therapy after menopause mitigates effects of stress on cortisol and working memory. J Clin Endocrinol Metab 102:4457–4466.

134. Almela M, Hidalgo V, Villada C, Espin L, Gomez-Amor J, Salvador A (2011): The impact of cortisol reactivity to acute stress on memory: Sex differences in middle-aged people. Stress 14:117–127.

135. Hodes GE, Shors TJ (2005): Distinctive stress effects on learning during puberty. Horm Behav 48:163–171.

136. Hodes GE, Shors TJ (2007): Learning during middle age: A resistance to stress? Neurobiol Aging 28:1783–1788.

137. Shors TJ, Falduto J, Leuner B (2004): The opposite effects of stress on dendritic spines in male vs. female rats are NMDA receptor-dependent. Eur J Neurosci 19:145–150.

138. Tzeng WY, Wu HH, Wang CY, Chen JC, Yu L, Cherng CG (2016): Sex differences in stress and group housing effects on the number of newly proliferated cells and neuroblasts in middle-aged dentate gyrus. Front Behav Neurosci 10:249.

139. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D (2006): Depression and risk for Alzheimer disease: Systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry 63:530–538.

140. Singh-Manoux A, Dugravot A, Fournier A, Abell J, Ebmeier K, Kivimaki M, et al. (2017): Trajectories of depressive symptoms before diagnosis of dementia: A 28-year follow-up study. JAMA Psychiatry 74:712–718.

141. Mirza SS, Wolters FJ, Swanson SA, Koudstaal PJ, Hofman A, Tiemeier H, et al. (2016): 10-year trajectories of depressive symptoms and risk of dementia: A population-based study. Lancet Psychiatry 3:628–635.

142. Mielke MM, Vemuri P, Rocca WA (2014): Clinical epidemiology of Alzheimer's disease: Assessing sex and gender differences. Clin Epidemiol 6:37–48.

143. Seshadri S, Wolf PA, Beiser A, Au R, McNulty K, White R, et al. (1997): Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham Study. Neurology 49:1498–1504.

144. Dal Forno G, Palermo MT, Donohue JE, Karagiozis H, Zonderman AB, Kawas CH (2005): Depressive symptoms, sex, and risk for Alzheimer's disease. Ann Neurol 57:381–387.

145. Maccari S, Darnaudery M, Morley-Fletcher S, Zuena AR, Cinque C, Van Reeth O (2003): Prenatal stress and long-term consequences: implications of glucocorticoid hormones. Neurosci Biobehav Rev 27:119–127.

146. Babb JA, Carini LM, Spears SL, Nephew BC (2014): Transgenerational effects of social stress on social behavior, corticosterone, oxytocin, and prolactin in rats. Horm Behav 65:386–393.

147. Kanatsou S, Ter Horst JP, Harris AP, Seckl JR, Krugers HJ, Joels M (2015): Effects of mineralocorticoid receptor overexpression on anxiety and memory after early life stress in female mice. Front Behav Neurosci 9:374.

148. Nephew BC, Febo M, Huang W, Colon-Perez LM, Payne L, Poirier GL, et al. (2018): Early life social stress and resting state functional connectivity in postpartum rat anterior cingulate circuits. J Affect Disord 229:213–223.