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Sex differences in vulnerability and resilience to stress across the lifespan

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Abstract

Susceptibility and resilience to stress depend on the timing of the exposure with respect to development, when across the lifespan effects are measured, and the behavioral or biological phenotype under consideration. This translational review examines preclinical stress models providing clues to causal mechanisms and their relationship to more the 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 pre-natal period and early post-natal life put males at risk of developing diseases involving socialization, attention and cognition, such as autism spectrum disorders, and attention deficit disorder, respectively. While females show resilience to some of the proximal effects of pre-natal/early post-natal stress there is evidence that risk associated with developmental insults is unmasked in females following periods of hormonal activation and flux including puberty, pregnancy and perimenopause. Likewise, stress exposures during puberty have stronger proximal effects on females including an increased risk of developing mood- and stress-related illnesses such as depression, anxiety and, post-traumatic stress disorder. Hormonal changes during menopause and andropause impact the processes of memory and emotion in both sexes, though females are preferentially at risk for dementia and childhood adversity impacts estradiol effects on neural function. We propose that studies to determine mechanisms for *stress risk and resilience* across the lifespan must consider the nature and timing of stress exposures as well as the sex of the organism under investigation.

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Disclosures

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Keywords

mood disorders; stress; sex differences; epigenetics; estrogens; CRF

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 controls. In clinical research, the ability to experience significant stress(es) 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. That many individuals suffer psychopathology in the setting of acute stress, but fully recover, highlights the complexity of risk and resilience research in humans.

Biological and behavioral adaptations in response to stress along with nurturing environments mitigate the adverse effects of significant stress in rodent, primate and human subjects research (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 promote 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 prior to the emergence of frank symptoms (11). Finally, the majority of basic research examining the mechanisms of resilience has done so only in male animals (12) when the majority of humans experiencing stress-related disorders are female (13, 14).

We examine the concept of resilience as both a proximal and distal response to stress. We are defining proximal as responses measured within the same developmental epoch as the stress exposure and distal as responses that occur in a subsequent developmental time point. We discuss work with similar measurable endpoints from basic and clinical research examining sex differences in vulnerability and resilience of response to stress across the lifespan (Figure 1). We propose that resilience is an active and dynamic process that is shaped, in part by genetic sex, gonadal 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 trans-generational mechanisms. Human offspring exposed to extreme gestational stress such as 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 out 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, but not male, 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 pre-eclampsia [32]. 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 males exposed to maternal asthma and other medical adversities such as pre-eclampsia (22-24). Male risk bias is thought to be secondary to male adaptations in placental blood flow allowing the male fetus continue to grow *in utero,* but be born with greater peripheral vasodilation, a condition associated with worse neonatal outcome [32]. However, the timing of the stress exposure during gestation also contributes to sex differences on 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 have been linked to increased risk of schizophrenia and autism spectrum disorders (26-29). Similarly, rodent models of maternal immune activation or stress demonstrate lasting effects predominantly on male offspring's behavior (30-33) although effects are also reported in females (Table 1) (34-37). There is evidence of greater distal effects of prenatal stress in females on subsequent stress related behavior and physiology responses later in life (38). Later gestational stress or cytokine exposure (PND 11- parturition) leads to greater behavioral changes in females than males (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, pre-clinical 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 (DNMT 1) involved in maintenance methylation and respond to maternal variable stress respond with a further increases supporting the likelihood of continued recreation of methylation patterns (35). Additionally, prenatal stress only impacts de novo methylation patterns in the brains of the male offspring resulting in changes of methylation status of the corticotropin releasing factor

(CRF) promoter and glucocorticoid receptor (GR) promoter in the hypothalamus (35) that contribute to lifelong changes in stress hormone signaling.

The epigenetic impact of prenatal stress on the offspring is not limited to stressors that affect the mother. Nor do stressors have to occur during gestation. Rodent studies in which either females or males were stressed during the peripubertal window, prior to 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 males found that stress and/or exposure to drugs of abuse produce lasting epigenetic changes in sperm (46, 47) that impact the offspring behavior (Table 1) (46-49).

In humans, maternal exposure to famine prior to concieving 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 F1 generation, but the adverse impact of the Holocaust on grandchildren's mental health appears less pronounced (51-53). While 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, recent data 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, female pre-pubertal exposure to the Holocaust effected transmission of risk phenotype to the offspring. Reduction in activity of the enzyme 11ß-hydroxysteroid dehydrogenase type 2 (11ß-HSD) 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 suffered in the Holocaust was more pronounced with respect to offspring 11ß-HSD activity if the mother was pre-pubertal at the time and her subsequent offspring was male (55).

Stress across the lifespan: Proximal and Distal Ramifications

Early life stress:

Studies of children isolated in orphanages due to previous polices 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 towards anxiety and depressive disorders and the male bias towards 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 males and females 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 socio-emotional 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 the age of 18 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 females 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). Males but not females have cognitive deficits that become more pronounced in males as they age (70). Decreased ability to perform cognitive tasks in these males were 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 care-giving stress on inflammation and telomere length, a marker of cellular aging (73) and older females are more likely to be caregivers than males. Women are also at roughly twice the risk of Alzheimer Disease than males (74). Severity of childhood trauma was associated with greater risk for a dementia diagnosis and Alzheimer Disease though sex differences were not investigated (75).

Pre-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 orthrodenticle homeobox 2 (OTX 2) contributed by mediating hedonic programming in the ventral tegmental area. A subsequent study in children (8-15) that have experienced childhood maltreatment found that the methylation status of peripheral OTX2 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 2 or more types of adversities during childhood-adolescence (age 0-18) using the Adverse Childhood Experiences (ACE) Questionnaire also showed a blunted HPA response to separation from their 6 month-old infants that was mirrored by the offspring who underwent a restraint and noise stressor (78). Sample size was too small to examine

offspring sex differences and it is unclear whether the blunted maternal and infant cortisol response to stress is a sign of risk or resilience. 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 childhood adversities are also more likely to experience a first onset of major depressive disorder during the perimenopause transition compared to those who reported no childhood adversities. Experience of 1 type of adversity during the pre-pubertal window was associated with resilience to depression even if the individual went on to experience additional childhood adversities during the post-pubertal 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. Non-human primate studies of social subordinant stress (82) and recent neuroimaging studies in postmenopausal females (83) suggest that early life stress is associated with enduring alterations estradiol driven changes on serotonergic functioning and may underlie a risk for depression or cognitive decline during periods of hypogonadism in females (84). Whether this same relationship holds true for older males is not known, but it is important to consider that adult males do not typically undergo a dramatic change in gonadal steroids with aging. Those males who experience natural or iatrogenically-induced hypogonadism are also at greater risk for cognitive declines and depression, though 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 half of the people who will experience mental illness have had their first occurrence and this figure rises to 75% by age 24 (88). In girls, early onset of menstruation (prior to 11.5) increases circulating levels of estrogens during adolescence and increases the risk of depression (89). While 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 compliment on gene expression in the frontal cortex of the four core genotype 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 GABA, serotonin and dopamine signaling in the frontal cortex (90). XY mice in the absence of testosterone expressed increased anxiety associated behavior compared to XX mice. Testosterone administration was anxiolytic indicating that the higher levels found in males 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 males in the basal lateral amygdala (91). Future work should examine distal effects of stress within this model along with earlier life stress exposure.

Pre-clinical research indicated that there are proximal neuroendocrine changes in stress reactivity and sex differences in behavior (Table 1) as an individual moves from the pre-pubertal state to early adulthood (98-103). The effects of stress during puberty are long lasting and have implications for the human development of PTSD and other stress based mood disorders (104). During adolescence girls are 3 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. Females 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) are more likely to engage in self-blame and avoidance whereas traumatized boys tend to report intrusive or re-experiencing symptoms (107). When non-traumatized 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. A finding not observed in traumatized women without PTSD and non-trauma controls (109). In healthy adult women, low estradiol levels are also associated with stronger intrusive memories in an experimental paradigm (110). 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 animal. Female 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 only occurs in females (113). Ovariectomy blocks the behavioral responses to 6 days of stress (114), it has not known whether gonadectomy also blocks the effects of longer periods of variable stress in females, nor 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 males, submissive behavior following conditioned defeat was dependent upon testosterone. Castrated males express more submissive behavior following fewer attacks. Testosterone or dihydrotestosterone replacement reduced submissive behavior in castrated males (116). Studies of social stress of young adult mice also indicate a neuromodulatory role for hormones, as estrogen receptor alpha (ER-α) expression was functionally linked to resilience. Male mice that were susceptible to social defeat stress had decreased ER-α expression in the nucleus accumbens (NAc) and increasing expression of ER-α promoted resilience (117). Nuclear ER-α expression was also decreased in NAc of male and female mice that underwent variable stress and over-expression promoted resilience in both sexes (117). Different transcriptional targets were regulated in males and females following over-expression of ER-α indicating that different downstream molecular

mechanisms regulate resilience in males and females. Molecular sex differences in response to stress have been replicated in other species including Syrian hamsters (118) and post-mortem 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 females. Gene ontogeny identified the CRF pathway shifting most towards a male transcriptional pattern. Viral mediated overexpression of DNMT3a made males and females responsive to sub-threshold variable stress and micro defeat (111, 119). Post-mortem NAc 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 due to decreased methylation of the CRF promoter (120). Antidepressant treatment blocks CRF promoter methylation and social anhedonia, whereas infusion into the hypothalamus of short interfering RNA (siRNA) 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 impacts attention and cognitive function in adult males but not females. Males are more sensitive to cholinergic CRF activation whereas females respond with a noradrenergic mediated hyper arousal 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 though 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. That males 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 males 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 two year period (130). 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 negatively sensitize cognitive and behavioral response to stress while 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 ages 54 to 72, only females showed a negative impact of a stressor on verbal memory. Women in the age group are likely to be postmenopausal and again cortisol levels were associated with worse performance in females only (134).

While 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 aged animals compared to young (Table 1)(135, 136) and these effects are in part mediated by sex specific NMDA receptor dependent changes in CA1 spine density (137). Acute stress also decreased cell proliferation in the hippocampus of female but not male aged 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 females 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 to young stressed females. Based on the clinical literature there is a genuine unmet need to examine the mechanisms through which hormones interact with stress in both sexes to promote cognitive and emotional resilience an individual ages.

It was originally proposed that depression during the lifespan was a risk factor for Alzheimer's disease (AD) as a earlier meta-analysis showed a significant correlation between the duration of time between depression and AD diagnoses and risk for AD (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 a prodrome of dementia. Those 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 was associated with a 71% greater risk of dementia. Retrospective analysis of data over 28 years showed that differences in depression symptoms was apparent 11 years prior to the diagnosis of dementia with an accelerated increase in depressive symptoms occurring in the decade prior to dementia diagnosis (140). Similarly, increasing but not steady or declining depressive symptoms over a 10-year period was associated with increased risk for all cause dementia and AD (141). Like 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 males and female 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 males, but not females (144).

Conclusions

In summary, males are at greater risk of adverse proximal and some distal behavioral effects of gestational and early life stress, due to a lack of compensatory mechanisms and alterations in epigenetic regulation and organizational effects of hormones. The greatest distal impact of stress in males at all lifespan epochs seems to be on cognitive ability, particularly spatial learning and may contribute symptoms associated with autism spectrum disorder, attention deficit disorder and the relationship between depression and AD later in life. While females 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 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 distal effects of stress in females.

The impact of sex on risk and resilience to stress is complex, varying 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 as well as central and peripheral levels of gonadal steroids. Similarly, the negative effects of stress can be observed immediately in both animal and human models or endure for years without apparent health effects 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 combined with genetic sex differences are driving factors effecting stress susceptibility and resilience in animal models and are also implicated in complex human disease states. As pre-clinical and clinical research works towards 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 endpoints 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.

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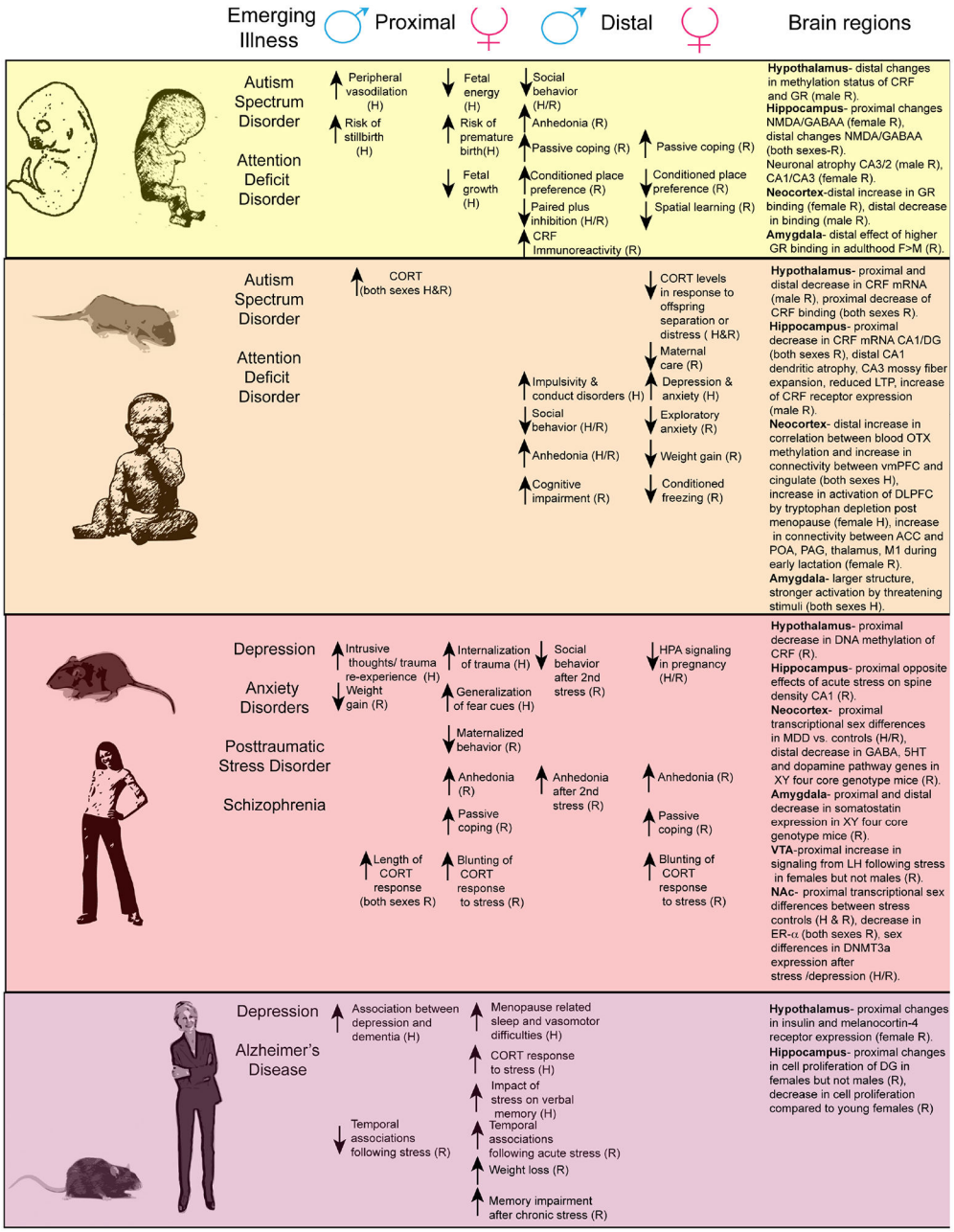

Figure 1. The relationship between stress effects on behavior across the lifespan and psychiatric disease

For each epoch of the lifespan 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 sub-regions. Abbreviations: N-methyl-D aspartate (NMDA), Gamma–Aminobutyric acid (GABA), ventral medial prefrontal cortex (vmPFC), dorsal lateral prefrontal cortex (DLPFC), anterior cingulated cortex (ACC), Preoptic area (POA), periaquaductal grey (PAG), Motor cortex 1 (M1), 5HT-serotonin, Lateral habenula (LH), dentate gyrus (DG).

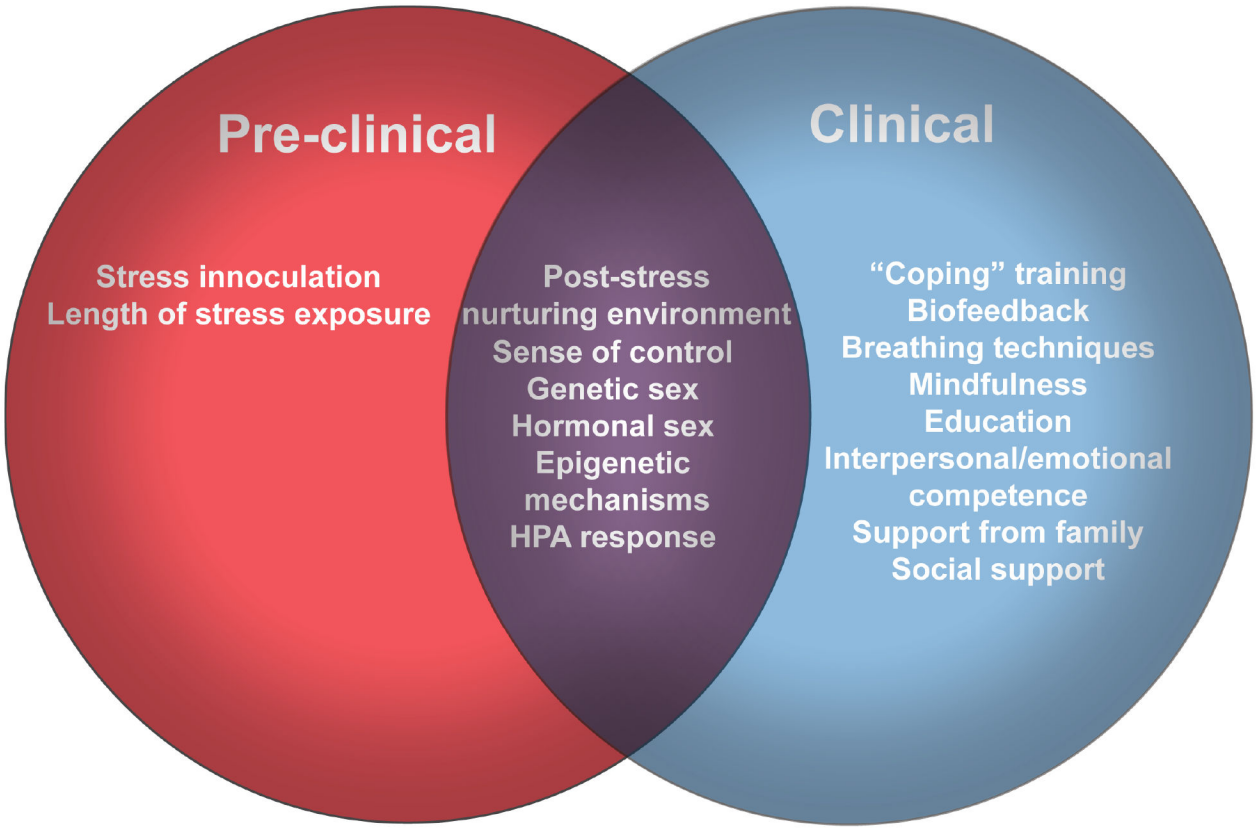

Figure 2. Methods and mechanisms of promoting resilience.

The Venn diagrams display methods of promoting resilience in animal models (red), human subjects (blue) and methods/mechanisms that translate across species (purple).

Table 1.

Sex differences in the effects of stress on HPA axis regulation and behavior in male and female preclinical studies across the lifespan.

Epoch of Stress exposure	Males	Females
Pre-conception	**Distal-** Increased anxiety/depression associated behaviors. Increased response to subsequent stress M > F (46, 48, 49).	**Distal-** Increased anxiety/depression associated behaviors. Increased response to subsequent stress M > F (46, 48, 49).
Pre-natal stress	**Distal-** Increased CORT in response to restraint (38). Decreased sociability and decreased paired plus inhibition (30-33). **PND1-7** **Distal -**Feminized patterns of spatial navigation in Barnes maze/increased immobility in FST (35). Passive coping/ anhedonia (34, 35). Decreased spatial learning (37) **PND 11- Birth** **Distal -**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)	**Distal-** Increased CORT, ACTH and corticosterone binding globulin in response to restraint (38). **PND 11- Birth** **Distal-** Passive coping (FST) M < F Decreased sensitivity to reward/ decreased conditioned place preference for chocolate/cocaine (40).
Birth- peri-puberty	**Proximal-** 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).	**Proximal-** Increased CORT Decreased growth (62-65). **Distal -**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). **Distal-** Increased submissive response to conditioned defeat (Syrian hamsters)(115).	**Proximal-** 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).
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)	**Proximal-** 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).	**Proximal-** No effect of stress on trace eyeblink conditioning (136). Decreased spatial learning (radial arm maze) (65).

Abbreviations: CORT- corticosterone; ACTH- adrenocorticotropic hormone; FST- forced swim test; NSF-novelty suppressed feeding