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Synthesizing Views to Understand Sex Differences in Response to Early Life Adversity

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Abstract

Sex as a biological variable (SABV) is critical for understanding the broad range of physiological, neurobiological, and behavioral consequences of early life adversity (ELA). The study of the interaction of SABV and ELA ties into several current debates, including the importance of taking into account SABV in research, differing strategies employed by males and females in response to adversity, and the possible evolutionary and developmental mechanisms of altered development in response to adversity. This review highlights the importance of studying both sexes, of understanding sex differences (and similarities) in response to ELA, and provides a context for the debate surrounding whether the response to ELA may be an adaptive process.

Keywords

Early life adversity; Early life stress; Sex differences; Evolution; Development; Sex as a biological variable

Identification of key questions and goals of this review

Inclusion of sex as a biological variable (SABV) in basic and translational neuroscience is critical [1]. Many neurological, neuropsychiatric, and stress-associated disorders have significant sex disparities in lifetime risk, presentation, and course of treatment [2-4]. Sex differences have been identified in side-effect profiles and risk associated with commonly prescribed and newly developed medication. However, few studies have tested for possible sex specific indications or warnings associated with the use of these drugs, or investigated the basis of sex differences in response [5-7]. The majority of studies investigating the biological underpinning of disorder, the development of new treatments, and the identification of risk factors have focused either exclusively on males or have failed to account for potential sex differences. Recent reviews have highlighted the importance of inclusion of SABV in research and identified ways to close this knowledge gap. Adding to

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this literature, inclusion of SABV is particularly relevant for understanding the impact of early life adversity (ELA) on brain development and later risk for pathology, and is the focus of this review.

To understand the importance of SABV in the context of ELA, several debates must be introduced. First, why has the study of females lagged behind work in males? Second, do the male and female brain differ, and if so, how? Following this, the term early life adversity will be defined, and the importance of the type and timing of adverse experiences will be addressed. Next, theories surrounding ELA associated changes in neurobehavioral development will be discussed, placing them in the context of evolutionary pressures supporting sex differences in response to ELA and their relation to theories of adaptation and pathology. And lastly, these topics will be brought together, with a discussion of recent work and future directions for the study of sex effects on response to ELA. The goal of this review is to synthesize ideas from several different areas and it borrows from and builds upon the excellent work and reviews of others. When relevant, the reader will be directed to resources providing a more thorough review of topics that cannot be fully developed in this piece.

Why is there a bias to study males in basic and translational research?

In a 2019 perspectives piece in *Science*, Dr. Rebecca Shansky elegantly addressed the historical rationale used by researchers to exclude female subjects from studies and focus selectively on males. This bias largely stemmed from the misperception that changes in circulating gonadal hormones associated with reproductive cycling in females increased variance and made females “messier and more variable than males” [8]. It is inarguable that manipulation of gonadal hormones profoundly impact behavior, molecular machinery underlying memory consolidation, neurodevelopment, metabolism, and brain activity [9,10]. However, empirical studies and meta-analysis of prior rodent work (one of the most commonly used model organisms) have found the argument of increased variability in females to be unfounded, with no differences in variance in males relative to females [11,12]. Based on such findings, several reviews have advocated for increased inclusion of females in basic and translational neuroscience, have provided guidelines and steps that can be taken to identify sex disparities in outcomes and have proposed strategies for appropriate comparison of sex-specific effects [8,13,14]. It should also be noted, that sex differences do not necessarily mean overt differences in phenotypic outcome, but can include utilizing different strategies, neural structures, or computations to support what appear to be common behaviors across sexes [14]. Thus, the inclusion of both males and females in basic and translational science is critical for the identification of differences, similarities, as well as disparate paths to the varied outcomes measured in research and clinical settings [14].

Biological sex impacts neurodevelopment

The descriptions that follow relate to modifiers of neurobehavioral development associated with biological sex and are separate from discussions of gender, a topic that deserves additional attention. At the most basic level, biological sex in mammalian systems is chromosomally determined, leading to Wolffian (male) or Mullerian (female) reproductive

tract development (reviewed in [15] and [16]). It has been argued that the differentiation of reproductive tissues into testes or ovaries drive sex differences in brain development that are the result of differences in the hormonal milieu derived from these reproductive tissues. More specifically, in the prenatal male there is a surge in testosterone that is believed to alter brain development through effects on neurogenesis and cell elimination, leading to the development of sexually dimorphic nuclei in an otherwise androgenous brain. The brain then undergoes further differentiation during adolescence, in response to male and female selective changes in gonadal hormones. While this classic theory is seductive, simplistic, and can explain some of robust changes in neuroanatomical and neurobehavioral development that have been observed, it is incomplete. Recent work has shown that sex, sexually dimorphic development, sex differences in the brain, and the signals that might drive such changes are far more complicated and go beyond organizational or activational hormonal effects [14,15].

In several excellent reviews, the authors highlight much of this new and exciting research [5,15-19]. The *Sry* gene, the gene on the Y chromosome that is largely responsible for masculinizing the development of the reproductive tract of males [20], also has direct transcriptional effects in neural tissue [21] and immune cells that impact neural development [22,23]. Thus, chromosomal differences between males and females have effects on gene expression that contribute to sex selective effects on neurodevelopment independent of, as well as in coordination with, hormonal drivers of sexual differentiation. Through a series of elegant studies, additional chromosomal and epigenetic drivers of neurodevelopment in the male and female brain have been identified. These include effects of parental genetic imprinting, epigenetic programming of gene expression, and sex differences in immune function and activation [22,23]. Genetic manipulation of the *Sry* gene has provides an experimental model that complements wild-type males and females: mice that have been genetically engineered to have the *Sry* gene silenced on the Y chromosome, leading to XY mice that develop reproductively as females; and mice genetically engineered to have the *Sry* gene expressed on the X chromosome, leading to XX mice that develop reproductively as males (known as the 4 core genotype mice). Work on these mouse lines has demonstrated a number of the aforementioned key principles. The Gestalt of this work is that chromosomal and epigenetic differences, in addition to hormonal effects, have complementary effects on neurogenesis, circuit assembly, pruning, plasticity, timing of neurodevelopmental events, and gene expression [14,15,24]. These differences alter the development and sensitivity of the constellation of cells in the brain (neural, glial, vascular, and immune) to both internal signals (hormonal, neural, and immune) and external ones (pre and postnatal environment). Further, sex selective somatic and early behavioral development primes the system to either elicit or receive disparate signals from the external environment, supporting further divergent (or convergent) effects on sexual differentiation of brain and behavior.

In coordination with early genetic and hormonal drivers of sexual development, the pre- and postnatal environments can also impact sex differences in brain development. The early environment affects the epigenome, gene expression, learning and memory, and cognitive and behavioral development. During gestation, changes in immune activation or circulating gonadal or stress hormones can alter the epigenome of the developing fetus and

consequently later behavior [25-27]. Further, in species that simultaneously gestate multiple fetuses, the position of the developing fetus can expose it to the gonadal hormones of the flanking fetuses, with cascading effect that lead to later pubertal onset and altered sexual behavior [28,29].

Significant sex disparities in early postnatal care also exist across species. In humans, sex differences have been identified in child-directed signals and care. Females receive higher levels of infant directed speech [30] and males receive greater quantity, and differences in the type of care (e.g. touching, holding, and soothing) during early development [31,32]. Sex differences in early care are not likely the result of human constructs of gender stereotyped responses to an infant, as similar differences can be observed across a range of species. In laboratory rodents, sex disparities have been found in the level of grooming provided to male relative to female pups, with males receiving significantly higher levels of anogenital licking [33-35]. The increased care directed toward males is thought to stimulate sexually dimorphic brain development and maturation of structures supporting reproduction [36-38]. Elegant work by Champagne, Meaney, Frances (and others) has demonstrated the importance of early life contact and care on epigenetic programming of the brain, with consequences for behavioral development. In rats, the level of care is predictive of later expression of anxiety-like behaviors and the programming of future maternal and reproductive behaviors, effects that can be transmitted across generations [39-42]. In non-human primates, and humans, levels of early life contact and quality of care are critical for early attachment, emotional development, cognitive development, social and socio-sexual development, and later risk for pathology [43-48].

Sex differences are also apparent in the distribution and form of ELA experienced during early life. Rearing rats in environments that lack adequate nesting material leads to increased incidence of abusive-like care, with females receiving higher levels of rough handling, biting, and dragging compared with male littermates [49]. Significant sex disparities in the incidence of early abuse have also been identified in humans, with females being at greater risk for sexual and some forms of physical and psychological abuse [50,51]. It should be noted that sex disparities may depend upon the developmental window being assessed (early versus late childhood) and the profile of the perpetrator [52]. Further, some sex disparities in ELA may be short in duration, with the effects of sex on maternal contact and speech being present principally during the first 4 months [31]. The significant sex disparities in either parent directed or infant elicited care, and differences in rates of abusive or negligent caregiving, can have profound effects on the development of the brain, serving to further drive sex selective effects on developmental trajectories, altered behavioral development, and risk for pathology.

Finally, significant sex disparities also exist in the timing of somatic and neural development. Effects of sex have been shown to be present for growth rate, impacting the timing of somatic growth, growth spurts, puberty onset, and brain development. As an example, in humans, sex differences have been reliably found for the timing of cortical maturation, myelination, and fiber tract development and refinement [53-59]. Given that the brain and bodies of males and females mature at different rates, environmental variables experienced at the same chronological age have the potential to impact disparate

neurodevelopmental processes, further impacting our understanding of the interaction of sex, developmental timing, and ELA on neural and behavioral development.

In summary, in addition to prenatal and pubertal gonadal hormone exposure, multiple intrinsic and extrinsic mechanisms exist that drive differences in male and female neurodevelopment. The differences in signals received by males and females from genetic, neuroendocrine, immune, and environmental sources, and the timing of those events, serve to support sex differences in brain development, with lasting consequences for behavior. Further, sex differences in the type of care received and risk for atypical or even abusive care can further increase the risk for sex differences in development and pathology. These findings alone provide a strong argument for the consideration of SABV in clinical, basic, and translational work and inclusion of both sexes in studies of ELA effects on brain and behavioral development, in addition to the broader considerations for emphasis on SABV as discussed in prior reviews.

Important variables to consider when studying early life adversity

The broader focus of this review is on the interaction between sex and early life adversity (ELA) on neurobehavioral development. However, the term adversity (as well as stress) can mean many things. In most ELA studies, the default has been to use the terminology early life stress (ELS). However, “stress” suggests that observed effects of a given manipulation are the result of engagement of the stress response, (e.g. sympathetic arousal, activation of the hypothalamic-pituitary-adrenal (HPA) axis, and rising stress hormone levels). While some ELA manipulations drive a “stress” response in either the parent and/or offspring, these experiences are much richer than merely the stress component. ELA is multifaceted and can come in the form of negative experience (abuse, trauma, pain, threat, and drug/toxicant exposure) the absence of experience (neglect, deprivation, thermoregulation, and food insecurity) or through species atypical experiences [60]. Disparate forms of ELA can impact the developing animal through engagement of stress-signaling or through the presence or absence of key experiential events that impact neural development, circuit assembly, or circuit refinement during early development (gestational or postnatal).

Highlighting the impact of a diverse array of early life experiences on a multitude of health outcomes, the adverse childhood experiences (ACE’s) study found ELA to be a risk factor for disorders that ranged from psychological wellbeing to cancer [61]. This work was critical in attracting attention to the importance of ELA for later risk for pathology. However, the ACE’s study focused on the number and not the type, timing, or duration of ELA on outcome. For epidemiological purposes, the cumulative effects of multiple forms of ELA can drive similar combinations of symptoms that show up within the syndromic definition of complex disorders such as depression. However, the specific type and timing of experiences may be critical for elevating risk for specific subsets of symptoms within the broader classification of a given pathology, as well as sex disparities in symptom development or presentation. In recent reviews [60,62], multiple groups have highlighted the importance of greater precision in the description of the type of adversity experienced and their unique impact on neural and behavioral outcomes. Further, considering the variety of processes supporting sexual differentiation of the brain and differences in the timing of brain

development described above, the type and timing of these varied experiences have the potential to elicit robust and sex selective effects on key outcomes, and may contribute to sex biases in risk for some forms of pathology. More work will be required, comparing and contrasting the effects of differing models of ELA, and their consequences on the developing male and female to better understand the unique contribution of each of these experiences to specific trajectories of neural and behavioral development.

Evolutionary recasting of the “toxic stress” response

ELA-associated changes in brain and behavioral development are commonly interpreted as resulting in a broken or pathological brain. This arises out of a focus on investigating “stress” effects on “deficits” in cognitive functioning, elevated risk for pathology, and morphological consequences of adversity on neuroanatomy. While ELA-associated effects can be devastating, debilitating, and are real, the question of whether these are the consequence of toxicity or are instead a byproduct of some other adaptation is at the focus of a growing debate. To truly understand the effects of ELA on brain and behavior, the effects of these experiences on the entire organism must be considered, as well as the potential short-term as well as long-term benefits and costs to the individual and to the species.

It is unlikely that evolution has selected for mechanisms that inflict damage on the individual in response to adversity, unless the effect subserves some other benefit for survival or reproduction. For example, the adult reaction to acute stress is to engage the fight or flight response. This includes a suppression of immune function and simultaneous mobilization of free energy to the bloodstream. This shift serves to support the proximate demands of the system (mobilizing energy to deal with an immediate threat) and diverts energy away from long-term demands (protecting from infection). Thus, it’s not that engagement of the HPA response is toxic to the immune system, or that stress is bad *per se*, but instead stress serves as a signal to change the priorities of the system to maximize biological resources to deal with the most pressing demand. However, repeated engagement of this system and the need to chronically adapt to environmental challenges, can have taxing effects on the sustained function of the system, with long-term negative consequences (e.g. stress adaptation and stress toxicity) [63-65]. Across development, similar trade-offs may occur in response to ELA, leading to differential investment of resources in somatic, brain, and/or behavioral development, with specific effects that depend on the sex of the developing organism.

In prior work, several labs have argued that changes in behavior or physiology in response to ELA may represent adaptation to the adverse rearing environment. This has resulted in the development of the theory that ELA drives a predictive adaptive response (PAR) [66-69]. In this theory, early environmental signals are sensed by the developing organism, and alter somatic and physiological development in anticipation of a given world (e.g. stress hormone exposure may alter brain development to increase vigilance). However, if the future environment fails to match the environment that was adapted for, increased vigilance may instead be interpreted as pathological anxiety [70]. Such effects have been observed across the ELA literature, with exposure to multiple forms of ELA being associated with behavioral profiles indicative of altered threat detection and elevated vigilance behaviors, with sex differences in expression (reviewed in [71]).

Synergistic with the PAR theory, early environmental signals may trigger adaptations to the rearing environment with proximate benefits to increase survival and reproduction (e.g. metabolic changes or effects on timing of reproductive development) but compromise longevity of the individual. Researchers have proposed the energetics theory (ET) [72,73] and psychosocial acceleration theory (PAT) [74] of development. In the energetics theory, the developing system senses the availability of resources and alters development to first maximize survival of the individual and secondarily to support reproduction. In this model, when resources are limited (e.g. poor nutrition, thermal challenge), available resources are devoted to development of brain and bodily functions that permit survival in the current environment. This may include delaying reproductive development in conditions that would not support the physiological demands of gestation or survival of offspring as well as possible reallocation of resources to promote development of limbic brain regions at the expense of cortical development. The PAT theory has similarities to the ET theory, in that signals associated with ELA are sensed by the developing organism and impact the timing of developmental processes. However, in the case of PAT, in the face of adversity, due to the anticipation of decreased longevity, development should occur more rapidly, to increase the probability of reaching reproductive maturity before death and passing on one's genes [75]. Unlike the ET theory, in the PAT theory, reproductive maturation would be accelerated in response to ELA, instead of delayed.

To date, most work testing these hypotheses has focused on ELA effects on the timing of reproductive maturation in females [76-78]. In humans, accelerated sexual maturation in females has been associated with prenatal stress, troubled family relations, mothers with mood disorders, higher allostatic load, and an absent father [77,79-85] (to name a few). Further, work has shown that higher socioeconomic status (SES), lower marital discord, and greater parental support were associated with decreased body mass and later sexual maturation [86]. Researchers have interpreted these findings to mean that in resource rich environments there is less pressure for early reproduction and a slower pace of life (POL), while more dangerous environments may promote an accelerated POL, consistent with the PAT theory. Still others have found that previously institutionalized (PI) children who were subsequently adopted into United States households did not demonstrate accelerated pubertal development [87], possibly due to the placement in resource rich environments, counteracting the impact of ELA on maturation. Similar rescue of ELA effects on precocious puberty have been found using environmental enrichment paradigms following ELA in rodent models. In 2018, Kenter and colleagues found that sensory enrichment blocked the precocious puberty that would otherwise result from a neonatal intensive care (NICU) model of ELA in rats [88]. Additional studies in animal models of ELA have found similar mixed effects of the form of ELA on timing of sexual maturation, with limited bedding and nesting (LBN) models leading to delays in somatic development and sexual maturation [89] and MS models as well as low licking and grooming models leading to earlier markers of puberty and altered timing of sexual maturation [41,90]. Few of these studies have tested for similar effects of ELA on the timing of reproductive maturation in males, who due to differing reproductive strategies to maximize success, may respond differently to ELA. While ELA effects on reproductive development may provide insights

into a subset of the effects of ELA on somatic and reproductive maturation, few studies have assessed the impact of ELA on timing of neural development.

Sex differences in adaptation to ELA

Across species, significant sex differences exist in the amount of investment (biological and behavioral) in reproduction, and differences in resources required for gestation and/or postnatal care, with females making greater investment in the developing offspring. This may have contributed to sex differences in the brain and body to support resource attainment, bonding, protection from the elements, and to provide a means of finding, attracting, and choosing mates with the greatest fitness (e.g. through production and sensing of visual, chemical, auditory, motor, and tactile signals of fitness). For example, in some species of birds there is regional specialization of the brain to support song learning, production, and reception. Sex differences in pressures to produce and receive these signals have driven sexually dimorphic brain development with males using song production for mate attraction and females evaluating song quality to select the best mate. In conditions of high adversity (limited resources, food scarcity, loss of habitat, predation risk, etc.), adaptations may act upon these systems to alter the production and sensing of these signals. For example, resource poor environments may drive changes in the vigor of song production and courting by males while simultaneously changing the threshold for females to choose a high quality song. In this instance, ELA effects on brain development should impact the male and female brain differently, and have regionally selective effects (e.g. divesting from development of cortical regions supporting the generation (males) and reception (females) of these signals and preserving or accelerating development of regions supporting approach and engagement in reproductive behaviors). To test this, the effects of ELA on brain development, and its consequences on multiple brain centers, must be measured simultaneously in both males and females.

ELA is associated with significant effects on timing of neural maturation

The effect of ELA on development goes beyond physical reproductive development and also impacts the timing of neural development [91]. Recent work in humans has shown that ELA in the form of institutional rearing is associated with precocious development of neural response to emotional stimuli in fMRI studies [92]. Work from Regina Sullivan and colleagues have found that stress hormone exposure or rearing in adverse environments resulted in precocious fear learning styles and earlier maturation of the amygdala in rats [93]. However, most of this work did not assess sex differences in response to ELA or expand to look beyond a single defined circuit. In experiments conducted in our lab, ELA in the form of limited access to nesting and bedding (LBN) altered the timing of maturation at the genetic, histological, and behavioral level, with disparate effects in males and females. LBN rearing led to accelerated hippocampus maturation in male mice [94]. In females, the acceleration of hippocampus maturation was less apparent and was not sustained (*unpublished data*). In the LBN model, sex selective effects on both neural and behavioral maturation depended upon the behavior and brain region being tested. LBN reared females, but not males, exhibited depressive-like behaviors [95], select deficits in attentional learning [96], accelerated amygdala maturation (*unpublished data*), delayed sexual maturation [89],

impaired contextual fear expression [97], and delayed development of select classes of cells in prefrontal cortex [96]. In male littermates, LBN led to select deficits in the development of object location learning [98], accelerated hippocampal and amygdala development [94], and shifts in the timing of cued and contextual threat learning [94]. Importantly, multiple neural and behavioral measures were shown to be less sensitive to the LBN manipulation. Together, this work has shown that multiple forms of ELA can alter the timing of neural and behavioral development. This work supports theoretical models of adaptation, showing that ELA can alter POL and timing of neural and behavioral development, accelerating limbic development and negatively impacting cortical maturation, with the magnitude and direction of effects depending on the sex of subject and region being assayed. Additional work from several labs has been adding to this important question [22,90,99-107]. However, more work will be needed to truly understand if the observed sex differences are the result of different strategies of adaptation, or differing experiences of the varied forms of ELA.

Interpreting sex differences in response to ELA

While work identifying sex differences in response to ELA at the neural and behavioral level has increased, a number of variables must be addressed to appropriately interpret those findings. First, a given manipulation may lead to fundamentally different experiences for males relative to females. In models manipulating maternal resources, parental care is altered for both sexes, but a sex bias may exist for the distribution of abuse, neglect, and preserved parental care. In models of separation, deprivation, handling, and bedding manipulation, females may receive greater levels of abuse while males receive higher levels of maternal contact [49]. This difference alone may contribute to sex differences in development. Second, most ELA manipulations are timed with males and females undergoing the manipulation simultaneously. However, sex differences have been identified in the timing of neurodevelopmental that may contribute to differences in sensitivity of males and females (e.g. ELA may disrupt migration and differentiation of subclasses of cells that have already matured in the other sex at the time of ELA). Third, epigenetic programming of development may confer differential sensitivity to exogenous cues. For example, the prenatal surge in testosterone in males may drive changes in epigenetic programming of genes involved in brain development, altering the sensitivity of the system the environmental signals of stress or adversity. Finally, it’s possible that evolution has selected for disparate strategies by which the male and female brain and body adapt to signals of adversity. In this case, adversity may drive altered development of neural structures guiding reproduction, aggression, and sensory-motor behavior that support the differing demands on males and females to promote reproductive success. Any, or all of these, could drive robust differences in brain and behavioral development and must be considered when interpreting sex differences in response to ELA.

In addition to understanding the variables that drive different responses of males and females to ELA, the assessment of developmental trajectories of multiple brain regions and multiple forms of behavior following ELA must be tested. While endophenotyping tasks are valuable for identifying disruption in a given behavior with known neural substrates, the demonstration of an effect of ELA on a given behavior does not mean that the observed effect on behavior was the goal of ELA associated changes in development. For example,

identification of ELA-associated effects on amygdala-dependent threat learning, does not necessarily mean that the goal of ELA was to alter vigilance behavior or threat associated learning. Multiple nuclei within the amygdala play critical roles in organizing socio-sexual behaviors, motivation, and supporting broader memory function. Effects of ELA on threat-learning may be a collateral effect of altered amygdala or circuit development to subserve benefit in some other function (e.g. reproduction). Thus, to truly understand the impact of ELA on brain and behavioral development it will be important to study the whole organism and the totality of the consequences of ELA on brain and body development. Without a broader context to interpret any given change, it may be inappropriate to conclude that the consequence of stress were to damage the brain.

Concluding Remarks

Moving forward, the gap in knowledge regarding sex differences in basic, clinical, and translational research must be closed. Understanding the contribution of SABV will be critical to understand the multitude of signals that can drive differences in male and female brain development, and alter the response to intrinsic and extrinsic signals. In this context, understanding the unique consequences of various forms of ELA on developmental process in males and females will help to understand basic principles of male and female brain development, and the ways in which males and females respond to experiential events, such as ELA. It will be important to broaden our focus to understand more global effects of ELA on neurobehavioral development and the impact of these changes on the functioning of the animal in the environment that it has developed to expect relative to the one that it is being tested in. These approaches will help guide a better understanding of the ways that brain and behavior change in response to ELA, the risks and benefits of those changes, and the ways in which each sex responds differently to those signals.

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Outstanding Questions

The varied forms of ELA result in differing outcomes across models, as well as across males and females. What are the unique effects of each form of ELA on development? Is the heterogeneity of results the consequence of different experiences of ELA, differing genetic programs for responding to it, differences in ontogenetic timing of males and females, varied hormonal signals, or some combination of these (and possibly other) factors?

A number of life history models have been developed to predict ELA effects on behavioral and reproductive development. What are the effects of ELA on trajectories of regional brain development in males and females? Do males and females differ in that respect? Do experimentally observed effects support the predictions of these models?

ELA studies have focused on adult outcomes and risk for “pathology”. By focusing instead on developmental processes (trajectories), can we better understand the neural underpinning of altered behavior of males and females? What do changes mean in the context of the ecological niche of the animal, the environment that was expected versus the one that was encountered, and the role of behavioral change for development, survival, and reproductive fitness of males relative to females?

Can findings from a single behavioral paradigm be interpreted in isolation from the more global effects of ELA? What additional systems (within and outside of the CNS) and behaviors should be surveyed in order to understand or interpret the cause or consequence of ELA effects on that circuit?

Many studies fail to identify sex differences in overt phenotypic outcomes, including in ELA studies, but does this mean that no sex difference exists? Further studies are warranted to understand the mechanism supporting similar behavioral profiles in males and females, as well as to test if there are shared or disparate paths to arriving at common phenotypic endpoints. Can we identify differing developmental trajectories, circuit recruitment, or neural computations supporting behaviors that appear to be the same in males and females?

Highlights

- Work to understand the impact of early life adversity (ELA) on female development has lagged behind work in males.
- A multitude of factors can drive different processes of brain development in males and females, potentially contributing to differential sensitivity to ELA.
- ELA effects on both males and females, likely serves as a signal to promote different trajectories of brain and behavioral development to enhance survival and reproductive success. However, it may do so by recruiting different processes in males relative to females.
- Greater precision in characterizing the signals that ELA provides to the developing organism, and better clarity about the broader consequences of ELA on the organism as a whole, will benefit our understanding of both the adaptive and detrimental effects of ELA on outcome measures.