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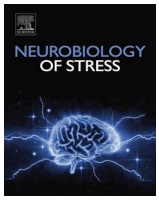

Early-life stress sensitizes response to future stress: Evidence and mechanisms

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ABSTRACT

Early-life stress sensitizes individuals to additional stressors and increases lifetime risk for mood and anxiety disorders. Research in both human populations and rodent models of early-life stress have sought to determine how different types of stressors contribute to vulnerability, and whether there are developmental sensitive periods for such effects. Although differences in the type and timing of rodent early-life stress paradigms have led to differences in specific behavioral outcomes, this complexity is present among humans as well. Robust rodent research now shows how early-life stress increases sensitivity to future stressors at behavioral, neural circuit, and molecular levels. These recent discoveries are laying the foundation for translation to more effective interventions relevant for those who experienced childhood stress and trauma.

Early-life stress (ELS) contributes to 30–40% of all adult-onset psychiatric disorders and suicide attempts worldwide (Green et al., 2010; Grummitt et al., 2024). In humans, ELS encompasses a wide variety of adverse experiences including: child maltreatment (i.e., neglect, physical abuse, psychological abuse); systematic stressors (e.g., poverty and racism); loss of a parent due to death, divorce, or incarceration; witnessing domestic or community violence; and loss of one's home (e.g., from family exclusion, poverty, natural disaster, or war-related displacement) (Cleary et al., 2018; Felitti et al., 1998; Luby, 2021; Masten and Narayan, 2012; Webb et al., 2024). There are numerous ways that investigators have attempted to understand the relationship between early experience and psychiatric disease risk based on number, type, or timing of experiences. There is robust evidence that simply experiencing more types of adverse childhood experiences (ACEs) leads to worse outcomes ("cumulative risk" hypothesis) (Felitti et al., 1998). Others have proposed that adverse experiences can be categorized along different dimensional gradients, such as threat, deprivation, or uncertainty (Brieant et al., 2023; McLaughlin and Sheridan, 2016). Studies have likewise sought to determine whether there are sensitive periods for experience of stress, or different sensitive periods for different types of stress (Dunn et al., 2013; Schaefer et al., 2022). Finally, research in humans and other animals shows that ELS sensitizes response to future stressors, leading to either a first appearance or synergistic worsening of psychiatric symptoms after additional stress (Hammen et al., 2000; Kendler et al., 2004; McGuigan and Middlemiss, 2005; McLaughlin et al., 2010; Peña et al., 2017, 2019a, 2019b; Saxton and Chyu, 2019). Recent research using rodent models of stress across the lifespan now provides the first mechanistic evidence for how ELS sensitizes response to future stressors at cellular and molecular levels.

1. Types and timing of stressors

1.1. Animal models of early-life stress

Animal models allow investigators to control variables related to type, timing, and accumulation of stressors, characterize the resultant molecular, cellular, and circuit-level changes in the brain, and functionally test the contributions of such changes to behavior. While early experimental research used non-human primate models of parental and social deprivation and demonstrated robust changes in neuroendocrine function and behavior akin to those observed among humans with mood and anxiety disorders (Ruppenthal et al., 1976; Sánchez et al., 2005; Young et al., 1973), rodent research has dominated the literature for the last several decades (Ader et al., 1960; Plotsky and Meaney, 1993) and has been the subject of thorough reviews (Murthy and Gould, 2018; Waters and Gould, 2022). In rodents, experience of reduced or disrupted maternal care (across a variety of rodent models) alters brain and behavioral outcomes consistent with ELS-attributable psychiatric disorders (Bolton et al., 2017; Duque-Quintero et al., 2022). Although differences in the type and timing of rodent ELS paradigms have led to differences in specific behavioral outcomes (Demaestri et al., 2020, 2022), this complexity is present among humans as well (Brieant et al.,

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2023). Foundational research showed that separating rat pups from their dams for 3 h per day from postnatal day (P) 2–14 disrupted the hypothalamic pituitary adrenal (HPA) axis into adulthood (Ader et al., 1960; Plotsky and Meaney, 1993). Studies of maternal separation or maternal deprivation (pups separated from their dams for a single 24-h bout) as a model of ELS dominated the literature until 2008, when a new model of limited bedding and nesting (LBN) emerged from the Baram lab (Ivy et al., 2008; Rice et al., 2008). Rather than deprive pups from their mother, this model of ELS allowed pups to stay with their dam but deprived them of resources in the home cage, which studies have shown to induce unpredictable maternal behavior (Demaestri et al., 2022). While it is difficult to map these rodent models of ELS onto the complex human experience, they likely disrupt normative rodent development in different ways.

Akin to the finding that multiple ACEs leads to worse outcomes, research has also combined maternal separation with limited nesting. C57Bl/6J mice exposed to this "multi-ACE" model from P10-20 (or P10-17) had relatively normal behavior in adulthood at baseline, but were hypersensitive to a second "hit" of stress and displayed exaggerated stress-related behavioral changes (Peña et al., 2017, 2019a, 2019b). This finding was in contrast to mice exposed to the same ten-day "multi-ACE" form of ELS from P2-12, whose response to adult stress was similar to control mice. The finding that late but not early postnatal stressors sensitized adult stress response was somewhat surprising given literature demonstrating HPA-axis sensitivity to challenges in this early postnatal period (Meaney and Aitken, 1985; Rice et al., 2008; Walker et al., 1986), but is in line with early literature showing that neonates show reduced ACTH and corticosterone responses to stress from P2-14, termed the stress hyporesponsive period (Butte et al., 1973; Guillet et al., 1980; Landers and Sullivan, 2012; Meaney et al., 1985). In rodents, endogenous corticosterone levels only become high enough to enable amygdala-dependent fear/avoidance learning around P10 and continue to increase to mature levels until P21 (Horii-Hayashi et al., 2013; Nishi et al., 2013; Rincón-Cortés and Sullivan, 2014). Interestingly, corticosterone response and amygdala-dependent fear learning are mediated by presence of the dam until P16 (and similarly in humans though adolescence: (Gee et al., 2014), such that the dam or even the dam's odor is able to reduce stress response and mitigate fear learning (Moriceau and Sullivan, 2006; Moriceau et al., 2009; Raineki et al., 2010, 2012). This finding also demonstrates the importance of maternal separation models in which pups are removed from the home cage away from comforting olfactory cues, rather than removing dams and leaving the pups in the home cage with comforting odors. Thus, because rodents (and indeed humans) are altricial and depend thoroughly on parental care for all aspects of survival in the first weeks (rodent) or years (human) of life, the early postnatal period can instead be thought of a period of *attachment sensitivity* during which survival is optimized if infants suppress stress response and attach to caregivers regardless of whether caregivers or the extended environment are adequate or stressful (Rincón-Cortés and Sullivan, 2014; Gee and Cohodes, 2021; Colombel et al., 2023).

1.2. Sensitive periods for the impact of early-life stress?

Stress is detrimental at any age and particularly so during development when stress can interact with development itself. While more challenging to delineate discreet periods of stress among humans, important work has attempted to determine whether there are sensitive periods for different kinds of stressors on different outcomes (Andersen et al., 2008; Dunn et al., 2018, 2019; Morrison et al., 2021; Zhu et al., 2022). Unexpected death of a parent at any point in childhood increased risk of depression; however losing a parent in early childhood (ages 0–5) was associated with the highest risk (Berg et al., 2016). Biologically, adversity — especially neighborhood disadvantage — during very early childhood (ages 0–3) also led to greater DNA methylation changes in peripheral blood leukocytes at age 7 compared to adversity experienced from ages 3–5 or 6–7 (Dunn et al., 2019), although adversity at older ages was not assessed. It is also important to note that loss of a parent is not reversible and neighborhood disadvantage is typically an ongoing exposure, and it is therefore not clear whether the higher risks associated with earlier loss and disadvantage are instead due to longer durations of adversity. Contrary to these findings, a number of studies point to *middle* childhood as a period of increased vulnerability for a broad range of mental health disorders. While children exposed to trauma at any age had higher emotion dysregulation, those exposed during middle childhood (ages 6–10) had the greatest emotional dysregulation compared to those who experienced trauma in early childhood (ages 0–5) or adolescence (ages 11–18) (Dunn et al., 2018). Similarly, neglect at age 10 was the most important predictor of later psychotic disorder (Schalinski et al., 2016, 2019), and physical abuse from 6 to 12 years old was associated with depression, anxiety, and PTSD, while abuse in early childhood or adolescence increased risk of PTSD but not depression or anxiety (Adams et al., 2018). However, a systematic review of the human literature did not converge on any single period of childhood most sensitive to childhood maltreatment (Schaefer et al., 2022). This may simply be due to the maturation of different systems being affected by stress at different ages, and the contributions of multiple brain systems to different aspects of stress response and psychiatric disease (Beck et al., 2025; Larsen et al., 2023; Sydnor et al., 2021, 2023). Rodent research shows that early postnatal stressors interact with development of olfactory, hypothalamic, thalamic, locus coeruleus, serotoninergic, and somatosensory systems (Birnie and Baram, 2022; Colombel et al., 2023; Kooiker et al., 2023; Packard and Opendak, 2022; Shionoya et al., 2007; Sullivan, 2001; Suri et al., 2015), while stressors after P10 engage amygdala and interact with later maturing systems including limbic and reward circuitry (Birnie et al., 2020; Hanson et al., 2015, 2021; Klune et al., 2023; Moriceau et al., 2009; Peña et al., 2017, 2019a, 2019b, 2025; Raineki et al., 2012; Rincón-Cortés and Sullivan, 2014; Waters and Gould, 2022; Yu et al., 2014).

An important and open question is then how developmental milestones in rodents map onto developmental milestones in humans. Some events, like the neonatal male testosterone surge, occur at birth in both rodents and humans (Gegenhuber and Tollkuhn, 2020). However, many other developmental milestones do not necessarily center around birth equally across species (Callaghan et al., 2019). This is observed most obviously for processes such as eye opening, which occurs in humans at birth but does not occur until P13-15 in mice (and which is slightly delayed with ELS; Demaestri et al., 2020). For cortical brain regions, research suggests that rodents are born relatively prematurely and the first week of a rodent's life is most similar to the last week of human gestation based on timing of dendritic development, synaptogenesis, myelination, and apoptosis (Chini and Hanganu-Opatz, 2021). However, other processes such as synaptic pruning and input/output connectivity may be better aligned to birth. Much more work is needed to better align these neurodevelopmental trajectories in different brain regions, especially in subcortical regions which may mature at different relative rates across species. While all of these ages and neural processes are important for shaping proper development and are vulnerable to stress in distinct ways, preclinical stress research should at least carefully consider how the timing of rodent manipulations maps onto human development (Luby et al., 2020).

2. Stress sensitization

2.1. Behavioral evidence of stress sensitization

ELS sensitizes response to future stressors, leading to either a first appearance or synergistic worsening of psychiatric symptoms after additional stress (Hammen et al., 2000; Kendler et al., 2004; McGuigan and Middlemiss, 2005; McLaughlin et al., 2010; Peña et al., 2017, 2019a, 2019b; Saxton and Chyu, 2019; Shapero et al., 2014; Sidamon-Eristoff et al., 2022; Starr et al., 2020; Wade et al., 2019). For example,

in a study of more than 34,000 adults, a history of ELS doubled the risk that stressors in the past year would lead to major depressive episodes (McLaughlin et al., 2010). This increased risk derives from increased sensitivity to (Kendler et al., 2004) and salience of stressful life events (Saxton and Chyu, 2019), such that exposure to at least one ACE lowers the threshold for additional stressful life events to lead to depression (Hammen et al., 2000). Experimental work in non-human primates confirms that maltreatment increases vigilance in both fear-evoking and neutral contexts (Howell et al., 2014), heightens emotional reactivity (McCormack et al., 2022), and augments behavioral and physiological responses to stress (Zhang et al., 2016).

In order to understand the neural correlates of hypersensitivity to future stressors, the impact of nine different early life manipulations spanning early postnatal through peri-adolescent periods was systematically evaluated on a battery of behavioral tasks in adult male mice, both at baseline and after a second stressor in adulthood (Peña et al., 2019a), namely chronic social defeat (Berton et al., 2006). Mice were tested for open field exploration, social interaction, and sucrose preference — representing distinct stress-sensitive behaviors — and evaluated on three criteria to determine the impact of two hits of stress. This effort revealed that the combination of maternal separation and limited nesting ELS from postnatal day P10-17, but not earlier from P2-12, sensitized male mice to experience of adult social defeat (Fig. 1) (Peña et al., 2017, 2019a). Similarly in female mice, combined maternal separation and limited nesting from P10-17, but not earlier, sensitized behavioral response to sub-threshold unpredictable variable stress in adulthood (Peña et al., 2019b). These results confirmed that ELS induces behavioral hypersensitivity to adult stress independent of the type of adult stressor, and that sensitive periods are similar for males and females. Interestingly, ELS did not significantly alter baseline male and female behavior, indicating that the impact of ELS on behavior is latent and revealed by adult stress exposure. This mouse model of ELS-induced stress sensitization has been replicated across a number of studies (Balouek et al., 2023; Bennett et al., 2024; Kronman et al., 2021; Parel et al., 2023; Guayasamin et al., 2025). Importantly, ELS has also been shown to sensitize response to subsequent stress in adolescence (and not just adulthood) in both human studies (Wade et al., 2019) and animal models (Huang et al., 2021).

2.2. Sensitization of cells and circuits by early-life stress

To determine whether ELS primes response to stress at a cellular level, we sought to understand whether neurons initially activated in response to ELS were reactivated by adult stress. Advances in transgenic mouse technology in the last decade now enable permanent experience-dependent tagging of cellular activity, which in turn allows investigators to track, manipulate, and isolate cells activated by a prior experience, such as ELS (DeNardo and Luo, 2017). We used one such strain to tag neurons activated during maternal separation (or during exploration of a novel enrichment object, an opposite-valence experience that activates similar numbers of neurons across brain regions) and test two hypotheses: (1) that adult stress activates overall more neurons given a history of prior ELS, or (2) that ELS-activated cells are preferentially reactivated by adult stress. We found evidence for the second preferential reactivation hypothesis in nucleus accumbens (NAc) and prefrontal cortex (PFC), but no evidence for the first hypothesis (Balouek et al., 2023). Furthermore, chemogenetically inhibiting activity of ELS-responsive NAc neurons, but not a similar number of control-tagged neurons, during experience of adult stress ameliorated behavioral response to stress (Balouek et al., 2023). Similarly, ELS in rats increases both basal and adult restraint stress-induced cFOS in ventral tegmental area (VTA) dopamine neurons, but not non-dopamine neurons of the VTA (Gugula et al., 2022). Increased dopamine neuron activity following ELS was specifically associated with elevated release of dopamine into the basolateral amygdala (BLA), which was found to be both necessary and sufficient for altered social behaviors (Opendak et al., 2021). ELS also increases cFOS response to adult restraint stress in orexin neurons of the lateral hypothalamus (LH), another brain region implicated in reward and motivated behaviors (Gugula et al., 2022). This effect may be driven primarily by males who have increased spontaneous firing of LH orexin

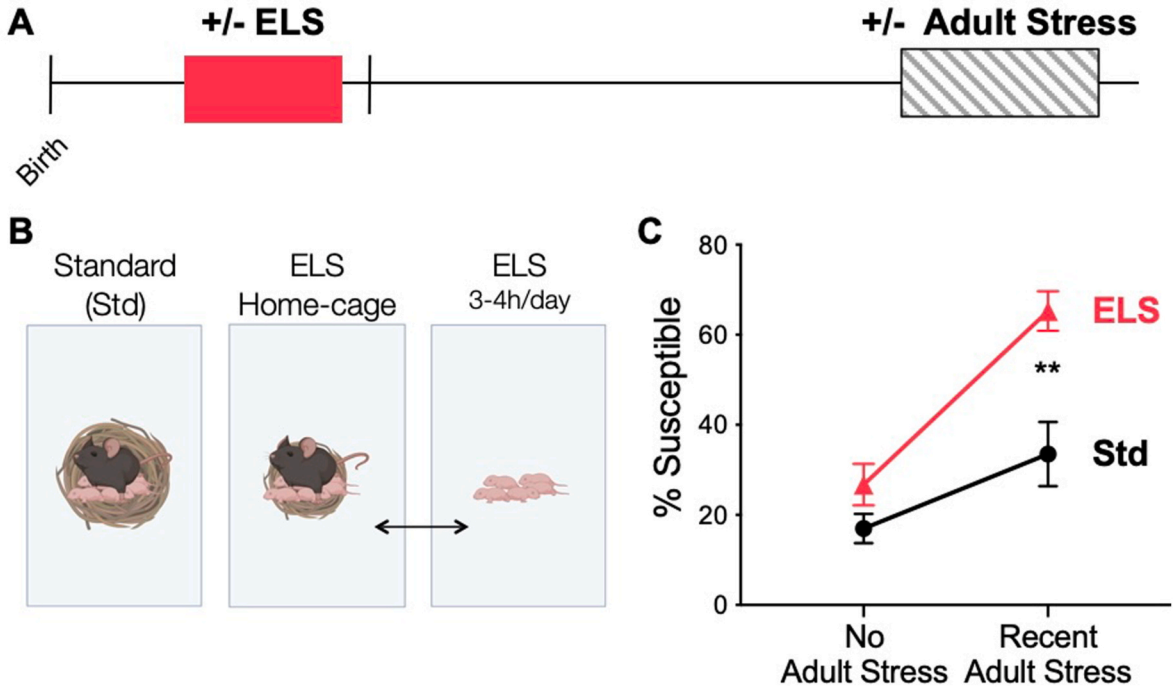

Fig. 1. Early-life stress sensitizes mice to stress in adulthood.
A) Paradigm, with early life stress (ELS) from P10-17. **B)** During "multi-ACE" ELS, mice have reduced nesting material in the home cage compared to standard-reared (Std) cages, and pups are separated to a clean cage for 3–4 h per day before reunion with their dam. **C)** ELS increases the proportion of male and female mice that show altered behaviors (e.g., social avoidance) in response to adult stress, across 10 cohorts.

neurons, while females have decreased spontaneous activity after ELS, although interestingly both of these changes are mediated by glucocorticoid-sensitive astrocytes (Depaauw-Holt et al., 2024). Together these studies provide evidence that ELS sensitizes neuronal response to adult stress across mesocorticolimbic circuitry.

Sensitized response to a second hit of stress is mediated by non-neuronal cells of the brain as well. ELS has been shown to have variable effects on astrocytes, which are the first cells to encounter signals from circulation (such as circulating glucocorticoid levels) and serve to regulate signaling of their neuronal neighbors (Abbink et al., 2019). Several studies show that ELS initially decreases astrocytes numbers in several brain regions, followed by a rebound and increase in astrocytes in adulthood (Abbink et al., 2020), although others report changes not in number of astrocytes but morphology such as decreased volume and processes following ELS, which are in turn associated with altered neuronal activity and ultimately behavior (Depaauw-Holt et al., 2024).

Microglia, the resident immune cells of the brain, are crucial to maintain proper synaptic balance among their neuronal neighbors and are likewise sensitive to ELS (Bolton et al., 2022). In both PFC and hippocampus, exposure to adult stress increased numbers of microglia only among mice previously exposed to ELS (Ferle et al., 2020). Cytokines, including PPARγ, were increased in the hippocampus following the combination of both ELS and adult stress (Ferle et al., 2020). However, ELS alters microglia number, morphology, subtype, and gene expression profiles across bran regions even prior to a second hit of stress (Bolton et al., 2022; Gildawie et al., 2020; Reemst et al., 2022). These ELS-induced microglia changes are associated with altered response to immune challenge in adulthood, reduced phagocytosis of neighboring neuronal synapses, and increased excitatory neurotransmission (Bolton et al., 2022; Reemst et al., 2022). Indeed, chemogenetic modulation of microglial activity was found to mediate altered response to threat following ELS (Bolton et al., 2022).

2.3. Sensitization of molecular programs by early-life stress

ELS-induced sensitization of cells and circuits to additional stress is encoded and maintained at a molecular level (Parel and Peña, 2020). Bulk-tissue RNA-sequencing in VTA, NAc, PFC, and hippocampus revealed that ELS induces long-lasting changes in gene expression across the transcriptome (Kos et al., 2023; Peña et al., 2017, 2019b). These gene expression changes were enriched for genes governing aspects of nervous system development and axon guidance, indicating that ELS alters brain development itself (Peña et al., 2019b). Interestingly, the combination of ELS and adult stress induced unique gene expression changes relative to either stress alone in both male and female mice (Peña et al., 2017, 2019b). Indeed, ELS primes a subset of genes such that expression changes are latent and only revealed by a second hit of stress (Peña et al., 2019b). In VTA, molecular changes were downstream of the transcription factor *Otx2* (orthodenticle homeobox 2), which is temporarily suppressed by ELS in mice (Peña et al., 2017). In humans, *OTX2* is significantly associated with depression risk in genome-wide association studies (Als et al., 2023) and childhood maltreatment and *OTX2* methylation is associated with altered functional connectivity within the brain and depression in children (Kaufman et al., 2018). Over-expression of *Otx2* in mouse VTA was sufficient to restore resilience, while transient knockdown in juveniles, but not adults, increased sensitivity to later social defeat stress, demonstrating a causal and temporal role for *Otx2* in VTA dopamine neurons to prime stress sensitivity (Peña et al., 2017). In hippocampus, single-cell RNA-sequencing similarly revealed that ELS primes transcriptional response to acute social defeat predominately in GABAergic cells and glutamatergic cells of the dentate gyrus, with less priming occurring in CA3 and CA1 neurons (Kos et al., 2023). Priming also appears to occur at the level of the hypothalamic-pituitary-adrenal axis, as hypothalamic FKBP51 protein (involved in sequestering glucocorticoid receptor and modulating cellular response to stress (Zannas et al., 2016); levels are significantly increased by the combination of ELS and chronic social defeat stress (Eskandari et al., 2023).

These long-lasting changes in gene expression and *potential* ("priming") are likely maintained at an epigenetic level, akin to a "molecular memory" of ELS. Epigenetic priming is a phenomenon through which an environmental cue alters the epigenome at enhancers (distal cis-regulatory regions of the genome) to facilitate a faster, stronger, or sensitized transcriptional response to subsequent exposures. Primed enhancers are in an open chromatin state more accessible to transcriptional machinery and marked by the post-translational chromatin modification histone-3 lysine-4 monomethylation (H3K4me1). Enhancers for genes being actively transcribed are distinguished by the additional chromatin modification histone-3 lysine-27 acetylation (H3K27Ac) (Bevington et al., 2016; Calo and Wysocka, 2013; D'Urso and Brickner, 2017; Lämke and Bäurle, 2017; Nguyen et al., 2015). Such stimulus-induced changes in enhancer state are argued to contribute to cell-wide "metaplasticity" — including both facilitated transcriptional response to subsequent stimuli and facilitated cellular activation (Griffith et al., 2024; Santoni et al., 2024). Indeed, ELS alters chromatin state via post-translational histone modifications in NAc (Kronman et al., 2021) and VTA (Geiger et al., 2024), and in both regions increases levels of H3K4me1 without altering H3K27Ac, supporting a role for epigenetic priming. Enriching for H3K4me1 by postnatal overexpression of the enzyme that "writes" this histone modification, *Setd7*, is sufficient to mimic ELS and sensitize transcriptional and behavioral response to mild adult social defeat stress (Geiger et al., 2024; Rashford et al., 2024). In VTA, epigenetic priming by *Setd7* overexpression and H3K4me1 enrichment sensitizes dopamine neuron firing after mild adult stress (Geiger et al., 2024), which is associated with stress susceptibility (Friedman et al., 2014), linking molecular and functional consequences of ELS. Whether enhancer priming following ELS leads to new or altered enhancer-promoter interactions during a second hit of stress is still under investigation. Together, these studies provide a mechanistic basis for how ELS sensitizes response to future stress at a molecular level.

3. Looking ahead: translating basic science

One goal of basic stress research is to inform potential medical interventions to either prevent disease onset in at-risk populations or most effectively treat disease after onset. While ELS heightens risk for mood, anxiety, substance-use, and other disorders, latent presentation of symptoms provides hope that intervention before onset is possible. Evidence that one main mechanism of increased risk is through increased stress sensitivity provides a focused and tractable target to reduce stress hypersensitivity to within normal range before mood and anxiety disorders take hold. There is some evidence from mouse models that even short-lasting interventions can be efficacious when done early. For example, transient viral overexpression of *Otx2* in juvenile VTA ameliorated response to later adult stress in mice (Peña et al., 2017), although it is unlikely that preventative gene therapy will ever be a realistic treatment. However, thyroid hormone signaling links the molecular cascade between ELS and suppressed *Otx2* (Chen et al., 2015), and is a highly translational target. Indeed, ELS transiently impinges on thyroid hormone signaling in mice (Bennett et al., 2024) and thyroid impairment was found among adolescents that experienced physical abuse or poverty (Machado et al., 2015). Intriguingly, *temporary* treatment with synthetic thyroid hormone (levothyroxine) following ELS in mice restores levels of some genes altered directly by ELS, prevented ELS-priming of other genes to adult stress, and rescued behavioral hypersensitivity to adult stress (Bennett et al., 2024). Additional basic research is needed to determine whether thyroid hormone treatment could be effective for preventing ELS-induced alterations in development and stress hypersensitivity in humans.

After onset, however, unique treatments may be needed for individuals who suffered from childhood adversity relative to the broader population. For example, depressed patients with a history of childhood

adversity have earlier onset of depression, more frequent episodes, increased recurrence, and traditional antidepressant treatments fail more often (Bernet and Stein, 1999; Nanni et al., 2012), suggesting that life history may delineate a unique sub-group of patients. Recent cross-species transcriptomic analyses revealed that ELS alters molecular patterning of the brain (here, NAc) to be more like molecular patterns associated with antidepressant treatment *failure* (Parel et al., 2023). However, transcriptomic profiling may also offer a key to identifying novel treatments that most effectively reverse molecular patterns of susceptibility and promote molecular patterns associated with resilience and treatment efficacy (Bagot et al., 2016).

While non-human animal models will never perfectly reproduce the full range and consequences of human experience of childhood aversity, concurrence across species on a growing list of molecular mediators of mood and anxiety disorder risk (e.g., *Otx2* and thyroid hormones discussed here; *Nr3c1* and *Fkbp5* reviewed in Matosin et al., 2018) provides hope that findings from animal models and advances in high-resolution molecular and systems neuroscience together can be translated to effective therapies relevant for those who experienced childhood stress and trauma (Gordon et al., 2024).

Declaration of competing interest

The authors declare no competing financial or personal interests.

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Data availability

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References

Abbink, M.R., Kotah, J.M., Hoeijmakers, L., Mak, A., Yvon-Durocher, G., van der Gaag, B., Lucassen, P.J., Korosi, A., 2020. Characterization of astrocytes throughout life in wildtype and APP/PS1 mice after early-life stress exposure. J. Neuroinflammation 17, 91. https://doi.org/10.1186/s12974-020-01762-z.

Abbink, M.R., van Deijk, A.-L.F., Heine, V.M., Verheijen, M.H., Korosi, A., 2019. The involvement of astrocytes in early-life adversity induced programming of the brain. Glia 67, 1637–1653. https://doi.org/10.1002/glia.23625.

Adams, J., Mrug, S., Knight, D.C., 2018. Characteristics of child physical and sexual abuse as predictors of psychopathology. Child Abuse Neglect 86, 167–177. https://doi.org/10.1016/j.chiabu.2018.09.019.

Ader, R., Tatum, R., Beels, C.C., 1960. Social factors affecting emotionality and resistance to disease in animals: I. Age of separation from the mother and susceptibility to gastric ulcers in the rat. J. Comp. Physiol. Psychol. 53, 446–454. https://doi.org/10.1037/h0044570.

Als, T.D., Kurki, M.I., Grove, J., Voloudakis, G., Therrien, K., Tasanko, E., Nielsen, T.T., Naamanka, J., Veerapen, K., Levey, D.F., Bendl, J., Bybjerg-Grauholm, J., Zeng, B., Demontis, D., Rosengren, A., Athanasiadis, G., Bækved-Hansen, M., Qvist, P., Bragi Walters, G., Thorgeirsson, T., Stefánsson, H., Musliner, K.L., Rajagopal, V.M., Farajzadeh, L., Thirstrup, J., Vilhjálmsson, B.J., McGrath, J.J., Mattheisen, M., Meier, S., Agerbo, E., Stefánsson, K., Nordentoft, M., Werge, T., Hougaard, D.M., Mortensen, P.B., Stein, M.B., Gelernter, J., Hovatta, I., Roussos, P., Daly, M.J., Mors, O., Palotie, A., Børglum, A.D., 2023. Depression pathophysiology, risk prediction of recurrence and comorbid psychiatric disorders using genome-wide analyses. Nat. Med. 29, 1832–1844. https://doi.org/10.1038/s41591-023-02352-1.

Andersen, S.L., Tomada, A., Vincow, E.S., Valente, E., Polcari, A., Teicher, M.H., 2008. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. J. Neuropsychiatry Clin. Neurosci. 20, 292–301. https://doi.org/10.1176/jnp.2008.20.3.292.

Bagot, R.C., Cates, H.M., Purushothaman, I., Vialou, V., Heller, E.A., Yieh, L., Labonté, B., Peña, C.J., Shen, L., Wittenberg, G.M., Nestler, E.J., 2016. Ketamine and imipramine reverse transcriptional signatures of susceptibility and induce resilience-specific gene expression profiles. Biol. Psychiatry 81, 285–295. https://doi.org/10.1016/j.biopsych.2016.06.012.

Balouek, J.-A., Mclain, C.A., Minerva, A.R., Rashford, R.L., Bennett, S.N., Rogers, F.D., Peña, C.J., 2023. Reactivation of early-life stress-sensitive neuronal ensembles contributes to lifelong stress hypersensitivity. J. Neurosci. 43, 5996–6009. https://doi.org/10.1523/JNEUROSCI.0016-23.2023.

Beck, D., Whitmore, L., MacSweeney, N., Brieant, A., Karl, V., de Lange, A.-M.G., Westlye, L.T., Mills, K.L., Tamnes, C.K., 2025. Dimensions of early-life adversity are differentially associated with patterns of delayed and accelerated brain maturation. Biol. Psychiatry, Stress, Allostasis, and Neurodev. 97, 64–72. https://doi.org/10.1016/j.biopsych.2024.07.019.

Bennett, S.N., Chang, A.B., Rogers, F.D., Jones, P., Peña, C.J., 2024. Thyroid hormones mediate the impact of early-life stress on ventral tegmental area gene expression and behavior. Horm. Behav. 159, 105472. https://doi.org/10.1016/j.yhbeh.2023.105472.

Berg, L., Rostila, M., Hjern, A., 2016. Parental death during childhood and depression in young adults – a national cohort study. JCPP (J. Child Psychol. Psychiatry) 57, 1092–1098. https://doi.org/10.1111/jcpp.12560.

Bernet, C.Z., Stein, M.B., 1999. Relationship of childhood maltreatment to the onset and course of major depression in adulthood. Depress. Anxiety 9, 169–174.

Berton, O., Mcclung, C.A., Dileone, R.J., Krishnan, V., Renthal, W., Russo, S.J., Graham, D., Tsankova, N.M., Bolaños, C.A., Rios, M., Monteggia, L.M., Self, D.W., Nestler, E.J., 2006. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science 311, 864–868. https://doi.org/10.1126/science.1120972.

Bevington, S.L., Cauchy, P., Piper, J., Bertrand, E., Lalli, N., Jarvis, R.C., Gilding, L.N., Ott, S., Bonifer, C., Cockerill, P.N., 2016. Inducible chromatin priming is associated with the establishment of immunological memory in T cells. EMBO J. 35, 515–535. https://doi.org/10.15252/embj.201592534.

Birnie, M.T., Baram, T.Z., 2022. Principles of emotional brain circuit maturation. Science 376, 1055–1056. https://doi.org/10.1126/science.abn4016.

Birnie, M.T., Kooiker, C.L., Short, A.K., Bolton, J.L., Chen, Y., Baram, T.Z., 2020. Plasticity of the reward circuitry after early-life adversity: mechanisms and significance. Biol. Psychiatry, Fear-Related Neuroplasticity and Anxiety Disorders 87, 875–884. https://doi.org/10.1016/j.biopsych.2019.12.018.

Bolton, J.L., Molet, J., Ivy, A., Baram, T.Z., 2017. New insights into early-life stress and behavioral outcomes - ScienceDirect. Current Opinion Behav. Sci. 14, 133–139. https://doi.org/10.1016/j.cobeha.2016.12.012.

Bolton, J.L., Short, A.K., Othy, S., Kooiker, C.L., Shao, M., Gunn, B.G., Beck, J., Bai, X., Law, S.M., Savage, J.C., Lambert, J.J., Belelli, D., Tremblay, M.-È., Cahalan, M.D., Baram, T.Z., 2022. Early stress-induced impaired microglial pruning of excitatory synapses on immature CRH-expressing neurons provokes aberrant adult stress responses. Cell Rep. 38, 110600. https://doi.org/10.1016/j.celrep.2022.110600.

Brieant, A., Vannucci, A., Nakua, H., Harris, J., Lovell, J., Brundavanam, D., Tottenham, N., Gee, D.G., 2023. Characterizing the dimensional structure of early-life adversity in the adolescent brain cognitive development (ABCD) study. Dev. Cognitive Neurosci. 61, 101256. https://doi.org/10.1016/j.dcn.2023.101256.

Butte, J.C., Kakihana, R., Farnham, M.L., Noble, E.P., 1973. The relationship between brain and plasma corticosterone stress response in developing rats. Endocrinology 92, 1775–1779. https://doi.org/10.1210/endo-92-6-1775.

Callaghan, B., Meyer, H., Opendak, M., Van Tieghem, M., Harmon, C., Li, A., Lee, F.S., Sullivan, R.M., Tottenham, N., 2019. Using a developmental ecology framework to align fear neurobiology across species. Annu. Rev. Clin. Psychol. 15, 345–369. https://doi.org/10.1146/annurev-clinpsy-050718-095727.

Calo, E., Wysocka, J., 2013. Modification of enhancer chromatin: what, how, and why? Mol. Cell 49, 825–837. https://doi.org/10.1016/j.molcel.2013.01.038.

Chen, C., Ma, Q., Chen, X., Zhong, M., Deng, P., Zhu, G., Zhang, Y., Zhang, L., Yang, Z., Zhang, K., Guo, L., Wang, L., Yu, Z., Zhou, Z., 2015. Thyroid hormone-otx2 signaling is required for embryonic ventral midbrain neural Stem cells differentiated into dopamine neurons. Stem Cell. Dev. 24, 150413084050007. https://doi.org/10.1089/scd.2014.0489.

Chini, M., Hanganu-Opatz, I.L., 2021. Prefrontal cortex development in health and disease: lessons from rodents and humans. Trends Neurosci. 44, 227–240. https://doi.org/10.1016/j.tins.2020.10.017.

Cleary, S.D., Snead, R., Dietz-Chavez, D., Rivera, I., Edberg, M.C., 2018. Immigrant trauma and mental health outcomes among latino youth. J. Immigr. Minority Health 20, 1053–1059. https://doi.org/10.1007/s10903-017-0673-6.

Colombel, N., Ferreira, G., Sullivan, R.M., Coureaud, G., 2023. Dynamic developmental changes in neurotransmitters supporting infant attachment learning. Neurosci. Biobehav. Rev. 151, 105249. https://doi.org/10.1016/j.neubiorev.2023.105249.

Demaestri, C., Gallo, M., Mazenod, E., Hong, A.T., Arora, H., Short, A.K., Stern, H., Baram, T.Z., Bath, K.G., 2022. Resource scarcity but not maternal separation provokes unpredictable maternal care sequences in mice and both upregulate Crh-associated gene expression in the amygdala. Neurobiol. Stress 20, 100484. https://doi.org/10.1016/j.ynstr.2022.100484.

Demaestri, C., Pan, T., Critz, M., Ofray, D., Gallo, M., Bath, K.G., 2020. Type of early life adversity confers differential, sex-dependent effects on early maturational milestones in mice. Horm. Behav. 124, 104763. https://doi.org/10.1016/j.yhbeh.2020.104763.

DeNardo, L., Luo, L., 2017. Genetic strategies to access activated neurons. Curr. Opin. Neurobiol. 45, 121–129. https://doi.org/10.1016/j.conb.2017.05.014.

Depaauw-Holt, L., Hamane, S., Peyrard, S., Rogers, B., Fulton, S., Bosson, A., Murphy-Royal, C., 2024. Astrocyte glucocorticoid receptors mediate sex-specific changes in activity following stress. https://doi.org/10.1101/2024.09.17.613499.

Dunn, E.C., McLaughlin, K.A., Slopen, N., Rosand, J., Smoller, J.W., 2013. Developmental timing of child maltreatment and symptoms of depression and suicidal ideation in young adulthood: results from the national longitudinal study of adolescent health. Depress. Anxiety 30, 955–964. https://doi.org/10.1002/da.22102.

Dunn, E.C., Nishimi, K., Gomez, S.H., Powers, A., Bradley, B., 2018. Developmental timing of trauma exposure and emotion dysregulation in adulthood: are there sensitive periods when trauma is most harmful? J. Affect. Disord. 227, 869–877. https://doi.org/10.1016/j.jad.2017.10.045.

Dunn, E.C., Soare, T.W., Zhu, Y., Simpkin, A.J., Suderman, M.J., Klengel, T., Smith, A.D. A.C., Ressler, K.J., Relton, C.L., 2019. Sensitive periods for the effect of childhood adversity on DNA methylation: results from a prospective, longitudinal study. Biol. Psychiatry, Longitudinal Perspectives on Stress and Depression 85, 838–849. https://doi.org/10.1016/j.biopsych.2018.12.023.

Duque-Quintero, M., Hooijmans, C.R., Hurowitz, A., Ahmed, A., Barris, B., Homberg, J. R., Hen, R., Harris, A.Z., Balsam, P., Atsak, P., 2022. Enduring effects of early-life adversity on reward processes: a systematic review and meta-analysis of animal studies. Neurosci. Biobehav. Rev. 142, 104849. https://doi.org/10.1016/j.neubiorev.2022.104849.

D'Urso, A., Brickner, J.H., 2017. Epigenetic transcriptional memory. Curr. Genet. 63, 435–439. https://doi.org/10.1007/s00294-016-0661-8.

Eskandari, F., Salimi, M., Binayi, F., Abdollahifar, M.-A., Eftekhary, M., Hedayati, M., Ghanbarian, H., Zardooz, H., 2023. Investigating the effects of maternal separation on hypothalamic-pituitary-adrenal Axis and glucose homeostasis under chronic social defeat stress in young adult male rat offspring. Neuroendocrinology 113, 361–380. https://doi.org/10.1159/000526989.

Felitti, V.J., Anda, R.F., Nordenberg, D., Williamson, D.F., Spitz, A.M., Edwards, V., Koss, M.P., Marks, J.S., 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. https://doi.org/10.1016/S0749-3797(98)00017-8.

Ferle, V., Repouskou, A., Aspiotis, G., Raftogianni, A., Chrousos, G., Stylianopoulou, F., Stamatakis, A., 2020. Synergistic effects of early life mild adversity and chronic social defeat on rat brain microglia and cytokines. Physiol. Behav. 215, 112791. https://doi.org/10.1016/j.physbeh.2019.112791.

Friedman, A.K., Walsh, J.J., Juarez, B., Ku, S.M., Chaudhury, D., Wang, J., Li, X., Dietz, D.M., Pan, N., Vialou, V.F., Neve, R.L., Yue, Z., Han, M.-H., 2014. Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. Science 344, 313–319. https://doi.org/10.1126/science.1249240.

Gee, D.G., Cohodes, E.M., 2021. Influences of caregiving on development: a sensitive period for biological embedding of predictability and safety cues. Curr. Dir. Psychol. Sci. 30, 376–383. https://doi.org/10.1177/09637214211015673.

Gee, D.G., Gabard-Durnam, L., Telzer, E.H., Humphreys, K.L., Goff, B., Shapiro, M., Flannery, J., Lumian, D.S., Fareri, D.S., Caldera, C., Tottenham, N., 2014. Maternal buffering of human amygdala-prefrontal circuitry during childhood but not during adolescence. Psychol. Sci. 25, 2067–2078. https://doi.org/10.1177/0956797614550878.

Gegenhuber, B., Tollkuhn, J., 2020. Signatures of sex: sex differences in gene expression in the vertebrate brain. WIREs Dev. Biol. 9, e348. https://doi.org/10.1002/wdev.348.

Geiger, L.T., Balouek, J.-A.R., Farrelly, L.A., Chen, A.S., Tang, M., Bennett, S.N., Nestler, E.J., Garcia, B.A., Maze, I., Peña, C.J., 2024. Early-life stress alters chromatin modifications in VTA to prime stress sensitivity. https://doi.org/10.1101/2024.03.14.584631.

Gildawie, K.R., Orso, R., Peterzell, S., Thompson, V., Brenhouse, H.C., 2020. Sex differences in prefrontal cortex microglia morphology: impact of a two-hit model of adversity throughout development. Neurosci. Lett. 738, 135381. https://doi.org/10.1016/j.neulet.2020.135381.

Gordon, J.A., Dzirasa, K., Petzschner, F.H., 2024. The neuroscience of mental illness: building toward the future. Cell 187, 5858–5870. https://doi.org/10.1016/j.cell.2024.09.028.

Green, J.G., McLaughlin, K.A., Berglund, P.A., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., Kessler, R.C., 2010. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I. Arch. Gen. Psychiatry 67, 113–123.

Griffith, E.C., West, A.E., Greenberg, M.E., 2024. Neuronal enhancers fine-tune adaptive circuit plasticity. Neuron 112, 3043–3057. https://doi.org/10.1016/j.neuron.2024.08.002.

Grummitt, L., Baldwin, J.R., Lafoa'i, J., Keyes, K.M., Barrett, E.L., 2024. Burden of mental disorders and suicide attributable to childhood maltreatment. JAMA Psychiatry. https://doi.org/10.1001/jamapsychiatry.2024.0804.

Guayasamin, M., Depaauw-Holt, L.R., Adedipe, I.I., Ghenissa, O., Vaugeois, J., Duquenne, M., Rogers, B., Latraverse-Arquilla, J., Peyrard, S., Bosson, A., Murphy-Royal, C., 2025. Early-life stress induces persistent astrocyte dysfunction associated with fear generalisation. eLife. https://doi.org/10.7554/eLife.99988.

Gugula, A., Trenk, A., Celary, A., Cizio, K., Tylko, G., Blasiak, A., Hess, G., 2022. Early-life stress modifies the reactivity of neurons in the ventral tegmental area and lateral hypothalamus to acute stress in female rats. Neuroscience 490, 49–65. https://doi.org/10.1016/j.neuroscience.2022.02.017.

Guillet, R., Saffran, M., Michaelson, S.M., 1980. Pituitary-adrenal response in neonatal rats. Endocrinology 106, 991–994. https://doi.org/10.1210/endo-106-3-991.

Hammen, C., Henry, R., Daley, S.E., 2000. Depression and sensitization to stressors among young women as a function of childhood adversity. J. Consult. Clin. Psychol. 68, 782. https://doi.org/10.1037/0022-006X.68.5.782.

Hanson, J.L., Hariri, A.R., Williamson, D.E., 2015. Blunted ventral striatum development in adolescence reflects emotional neglect and predicts depressive symptoms. BPS 78, 598–605. https://doi.org/10.1016/j.biopsych.2015.05.010.

Hanson, J.L., Williams, A.V., Bangasser, D.A., Peña, C.J., 2021. Impact of early life stress on reward circuit function and regulation. Front. Psychiatr. 12, 1799. https://doi.org/10.3389/fpsyt.2021.744690.

Horii-Hayashi, N., Sasagawa, T., Matsunaga, W., Matsusue, Y., Azuma, C., Nishi, M., 2013. Developmental changes in desensitisation of c-Fos expression induced by repeated maternal separation in pre-weaned mice. J. Neuroendocrinol. 25, 158–167.

Howell, B.R., Grand, A.P., McCormack, K.M., Shi, Y., LaPrarie, J.L., Maestripieri, D., Styner, M.A., Sanchez, M.M., 2014. Early adverse experience increases emotional reactivity in juvenile rhesus macaques: relation to amygdala volume. Dev. Psychobiol. 56, 1735–1746. https://doi.org/10.1002/dev.21237.

Huang, J., Shen, C., Ye, R., Shi, Y., Li, W., 2021. The effect of early maternal separation combined with adolescent chronic unpredictable mild stress on behavior and synaptic plasticity in adult female rats. Front. Psychiatr. 12. https://doi.org/10.3389/fpsyt.2021.539299.

Ivy, A., Brunson, K., Sandman, C., Baram, T., 2008. Dysfunctional nurturing behavior in rat dams with limited access to nesting material: a clinically relevant model for early-life stress. Neuroscience 154, 1132–1142. https://doi.org/10.1016/j.neuroscience.2008.04.019.

Kaufman, J., Wymbs, N.F., Montalvo-Ortiz, J.L., Orr, C., Albaugh, M.D., Althoff, R., O'Loughlin, K., Holbrook, H., Garavan, H., Kearney, C., Yang, B.-Z., Zhao, H., Peña, C., Nestler, E.J., Lee, R.S., Mostofsky, S., Gelernter, J., Hudziak, J., 2018. Methylation in OTX2 and related genes, maltreatment, and depression in children. Neuropsychopharmacology 356, 1185. https://doi.org/10.1038/s41386-018-0157-y.

Kendler, K.S., Kuhn, J.W., Prescott, C.A., 2004. Childhood sexual abuse, stressful life events and risk for major depression in women. Psychol. Med. 34, 1475–1482.

Klune, C.B., Goodpaster, C.M., Gongwer, M.W., Gabriel, C.J., Chen, R., Jones, N.S., Schwarz, L.A., DeNardo, L.A., 2023. Developmentally distinct architectures in top-down circuits. https://doi.org/10.1101/2023.08.27.555010.

Kooiker, C.L., Chen, Y., Birnie, M.T., Baram, T.Z., 2023. Genetic tagging uncovers a robust, selective activation of the thalamic paraventricular nucleus by adverse experiences early in life. Biol. Psychiatry: Global Open Sci. https://doi.org/10.1016/j.bpsgos.2023.01.002.

Kos, A., Lopez, J.P., Bordes, J., de Donno, C., Dine, J., Brivio, E., Karamihalev, S., Luecken, M.D., Almeida-Correa, S., Gasperoni, S., Dick, A., Miranda, L., Büttner, M., Stoffel, R., Flachskamm, C., Theis, F.J., Schmidt, M.V., Chen, A., 2023. Early life adversity shapes social subordination and cell type–specific transcriptomic patterning in the ventral hippocampus. Sci. Adv. 9, eadj3793. https://doi.org/10.1126/sciadv.adj3793.

Kronman, H., Torres-Berrío, A., Sidoli, S., Issler, O., Godino, A., Ramakrishnan, A., Mews, P., Lardner, C.K., Parise, E.M., Walker, D.M., van der Zee, Y.Y., Browne, C.J., Boyce, B.F., Neve, R., Garcia, B.A., Shen, L., Peña, C.J., Nestler, E.J., 2021. Long-term behavioral and cell-type-specific molecular effects of early life stress are mediated by H3K79me2 dynamics in medium spiny neurons. Nat. Neurosci. 1–10. https://doi.org/10.1038/s41593-021-00814-8.

Lämke, J., Bäurle, I., 2017. Epigenetic and chromatin-based mechanisms in environmental stress adaptation and stress memory in plants. Genome Biol. 18, 124. https://doi.org/10.1186/s13059-017-1263-6.

Landers, M.S., Sullivan, R.M., 2012. The development and neurobiology of infant attachment and fear. Dev. Neurosci. 34, 101–114. https://doi.org/10.1159/000336732.

Larsen, B., Sydnor, V.J., Keller, A.S., Yeo, B.T.T., Satterthwaite, T.D., 2023. A critical period plasticity framework for the sensorimotor–association axis of cortical neurodevelopment. Trends Neurosci. https://doi.org/10.1016/j.tins.2023.07.007, 0.

Luby, J.L., 2021. Elucidating neural mechanisms of poverty on child development leads back to psychosocial mechanisms. Biol. Psychiatry 90, 141–142. https://doi.org/10.1016/j.biopsych.2021.04.022.

Luby, J.L., Baram, T.Z., Rogers, C.E., Barch, D.M., 2020. Neurodevelopmental optimization after early-life adversity: cross-species studies to elucidate sensitive periods and brain mechanisms to inform early intervention. Trends Neurosci. 43, 744–751. https://doi.org/10.1016/j.tins.2020.08.001.

Machado, T.D., Salum, G.A., Bosa, V.L., Goldani, M.Z., Meaney, M.J., Agranonik, M., Manfro, G.G., Silveira, P.P., 2015. Early life trauma is associated with decreased peripheral levels of thyroid-hormone T3 in adolescents. Int. J. Dev. Neurosci. : the off. J. Int. Society Dev. Neurosci. 47, 304–308. https://doi.org/10.1016/j.ijdevneu.2015.10.005.

Masten, A.S., Narayan, A.J., 2012. Child development in the context of disaster, war, and terrorism: pathways of risk and resilience. Annu. Rev. Psychol. 63, 227–257. https://doi.org/10.1146/annurev-psych-120710-100356.

Matosin, N., Halldorsdottir, T., Binder, E.B., 2018. Understanding the molecular mechanisms underpinning gene by environment interactions in psychiatric disorders: the FKBP5 model. BPS. https://doi.org/10.1016/j.biopsych.2018.01.021.

McCormack, K.M., Howell, B.R., Higgins, M., Bramlett, S., Guzman, D., Morin, E.L., Villongco, C., Liu, Y., Meyer, J., Sanchez, M.M., 2022. The developmental consequences of early adverse care on infant macaques: a cross-fostering study. Psychoneuroendocrinology 146, 105947. https://doi.org/10.1016/j.psyneuen.2022.105947.

McGuigan, W.M., Middlemiss, W., 2005. Sexual abuse in childhood and interpersonal violence in adulthood: a cumulative impact on depressive symptoms in women. J. Interpers Violence 20, 1271–1287. https://doi.org/10.1177/0886260505278107.

McLaughlin, K.A., Conron, K.J., Koenen, K.C., Gilman, S.E., 2010. Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: a test of the stress sensitization hypothesis in a population-based sample of adults. Psychol. Med. 40, 1647–1658. https://doi.org/10.1017/S0033291709992121.

McLaughlin, K.A., Sheridan, M.A., 2016. Beyond cumulative risk: a dimensional approach to childhood adversity. Curr. Dir. Psychol. Sci. 25, 239–245. https://doi.org/10.1177/0963721416655883.

Meaney, M.J., Aitken, D.H., 1985. The effects of early postnatal handling on hippocampal glucocorticoid receptor concentrations: temporal parameters. Brain Res. 354, 301–304.
Meaney, M.J., Sapolsky, R.M., McEwen, B.S., 1985. The development of the glucocorticoid receptor system in the rat limbic brain. I. Ontogeny and autoregulation. Dev. Brain Res. 18, 159–164. https://doi.org/10.1016/0165-3806(85)90259-7.
Moriceau, S., Shionoya, K., Jakubs, K., Sullivan, R.M., 2009. Early-life stress disrupts attachment learning: the role of amygdala corticosterone, locus ceruleus corticotropin releasing hormone, and olfactory bulb norepinephrine. J. Neurosci. 29, 15745–15755. https://doi.org/10.1523/JNEUROSCI.4106-09.2009.
Moriceau, S., Sullivan, R.M., 2006. Maternal presence serves as a switch between learning fear and attraction in infancy. Nat. Neurosci. 9, 1004–1006. https://doi.org/10.1038/nn1733.
Morrison, K.E., Stenson, A.F., Marx-Rattner, R., Carter, S., Michopoulos, V., Gillespie, C. F., Powers, A., Huang, W., Kane, M.A., Jovanovic, T., Bale, T.L., 2021. Developmental timing of trauma in women predicts unique extracellular vesicle proteome signatures. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2021.08.003, 0.
Murthy, S., Gould, E., 2018. Early life stress in rodents: animal models of illness or resilience? Frontiers Behav. Neurosci. 12, 320. https://doi.org/10.3389/fnbeh.2018.00157.
Nanni, V., Uher, R., Danese, A., 2012. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. Am. J. Psychiatr. 169, 141–151. https://doi.org/10.1176/appi.ajp.2011.11020335.
Nguyen, M.L.T., Jones, S.A., Prier, J.E., Russ, B.E., 2015. Transcriptional enhancers in the regulation of T cell differentiation. Front. Immunol. 6. https://doi.org/10.3389/fimmu.2015.00462.
Nishi, M., Horii-Hayashi, N., Sasagawa, T., Matsunaga, W., 2013. Effects of early life stress on brain activity: implications from maternal separation model in rodents. Gen. Comp. Endocrinol. 181, 306–309. https://doi.org/10.1016/j.ygcen.2012.09.024.
Opendak, M., Raineki, C., Perry, R.E., Rincón-Cortés, M., Song, S.C., Zanca, R.M., Wood, E., Packard, K., Hu, S., Woo, J., Martinez, K., Vinod, K.Y., Brown, R.W., Deehan, G.A., Froemke, R.C., Serrano, P.A., Wilson, D.A., Sullivan, R.M., 2021. Bidirectional control of infant rat social behavior via dopaminergic innervation of the basolateral amygdala. Neuron. https://doi.org/10.1016/j.neuron.2021.09.041.
Packard, K., Opendak, M., 2022. Rodent models of early adversity: impacts on developing social behavior circuitry and clinical implications. Front. Behav. Neurosci. 16. https://doi.org/10.3389/fnbeh.2022.918862.
Parel, S.T., Bennett, S.N., Cheng, C.J., Timmermans, O.C., Fiori, L.M., Turecki, G., Peña, C.J., 2023. Transcriptional signatures of early-life stress and antidepressant treatment efficacy. Proc. Natl. Acad. Sci. USA 120, e2305776120. https://doi.org/10.1073/pnas.2305776120.
Parel, S.T., Peña, C.J., 2020. Genome-wide signatures of early life stress: influence of sex. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2020.12.010.
Peña, C.J., DeBerardine, M., Sullivan, K.E., 2025. Molecular heterogeneity and development of the ventral tegmental area. Current Opinion Behav. Sci. 61, 101478. https://doi.org/10.1016/j.cobeha.2024.101478.
Peña, C.J., Kronman, H.G., Walker, D.M., Cates, H.M., Bagot, R.C., Purushothaman, I., Issler, O., Loh, Y.-H.E., Leong, T., Kiraly, D.D., Goodman, E., Neve, R.L., Shen, L., Nestler, E.J., 2017. Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2. Science 356, 1185–1188. https://doi.org/10.1126/science.aan4491.
Peña, C.J., Nestler, E.J., Bagot, R.C., 2019a. Environmental programming of susceptibility and resilience to stress in adulthood in male mice. Frontiers Behav. Neurosci. 13, 272. https://doi.org/10.3389/fnbeh.2019.00040.
Peña, C.J., Smith, M., Ramakrishnan, A., Cates, H.M., Bagot, R.C., Kronman, H.G., Patel, B., Chang, A.B., Purushothaman, I., Dudley, J., Morishita, H., Shen, L., Nestler, E.J., 2019b. Early life stress alters transcriptomic patterning across reward circuitry in male and female mice. Nat. Commun. 10, 5098. https://doi.org/10.1038/s41467-019-13085-6.
Plotsky, P.M., Meaney, M.J., 1993. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. Mol. Brain Res. 18, 195–200. https://doi.org/10.1016/0169-328X(93)90189-V.
Raineki, C., Cortés, M.R., Belnoue, L., Sullivan, R.M., 2012. Effects of early-life abuse differ across development: infant social behavior deficits are followed by adolescent depressive-like behaviors mediated by the amygdala. J. Neurosci. 32, 7758–7765. https://doi.org/10.1523/JNEUROSCI.5843-11.2012.
Raineki, C., Moriceau, S., Sullivan, R.M., 2010. Developing a neurobehavioral animal model of infant attachment to an abusive caregiver. Biol. Psychiatry 67, 1137–1145. https://doi.org/10.1016/j.biopsych.2009.12.019.
Rashford, R.L., DeBerardine, M., Kim, H.J.J., Arzouni, N., Hirschfield, L.W., Oke, O.M., Bennett, S.N., Pena, C.J., 2024. Early-life stress alters postnatal chromatin development in the nucleus accumbens. https://doi.org/10.1101/2024.04.12.589272.
Reemst, K., Kracht, L., Kotah, J.M., Rahimian, R., van Irsen, A.A.S., Congrains Sotomayor, G., Verboon, L.N., Brouwer, N., Simard, S., Turecki, G., Mechawar, N., Kooistra, S.M., Eggen, B.J.L., Korosi, A., 2022. Early-life stress lastingly impacts microglial transcriptome and function under basal and immune-challenged conditions. Transl. Psychiatry 12, 1–13. https://doi.org/10.1038/s41398-022-02265-6.
Rice, C.J., Sandman, C.A., Lenjavi, M.R., Baram, T.Z., 2008. A novel mouse model for acute and long-lasting consequences of early life stress. Endocrinology 149, 4892–4900. https://doi.org/10.1210/en.2008-0633.
Rincón-Cortés, M., Sullivan, R.M., 2014. Early life trauma and attachment: immediate and enduring effects on neurobehavioral and stress axis development. Front. Endocrinol. 5, 33. https://doi.org/10.3389/fendo.2014.00033.
Ruppenthal, G.C., Arling, G.L., Harlow, H.F., Sackett, G.P., Suomi, S.J., 1976. A 10-year perspective of motherless-mother monkey behavior. J. Abnorm. Psychol. 85, 341–349.
Sánchez, M.M., Noble, P.M., Lyon, C.K., Plotsky, P.M., Davis, M., Nemeroff, C.B., Winslow, J.T., 2005. Alterations in diurnal cortisol rhythm and acoustic startle response in nonhuman primates with adverse rearing. Biol. Psychiatry 57, 373–381. https://doi.org/10.1016/j.biopsych.2004.11.032.
Santoni, G., Astori, S., Leleu, M., Glauser, L., Zamora, S.A., Schioppa, M., Tarulli, I., Sandi, C., Gräff, J., 2024. Chromatin plasticity predetermines neuronal eligibility for memory trace formation. Science 385, eadg9982. https://doi.org/10.1126/science.adg9982.
Saxton, K., Chyu, L., 2019. Early life adversity increases the salience of later life stress: an investigation of interactive effects in the PSID. J. Dev. Origins of Health Disease 147, 1–12. https://doi.org/10.1017/S2040174419000308.
Schaefer, J.D., Cheng, T.W., Dunn, E.C., 2022. Sensitive periods in development and risk for psychiatric disorders and related endpoints: a systematic review of child maltreatment findings. Lancet Psychiatry 9, 978–991. https://doi.org/10.1016/S2215-0366(22)00362-5.
Schalinski, I., Breinlinger, S., Hirt, V., Teicher, M.H., Odenwald, M., Rockstroh, B., 2019. Environmental adversities and psychotic symptoms: the impact of timing of trauma, abuse, and neglect. Schizophr. Res. 205, 4–9. https://doi.org/10.1016/j.schres.2017.10.034.
Schalinski, I., Teicher, M.H., Nischk, D., Hinderer, E., Müller, O., Rockstroh, B., 2016. Type and timing of adverse childhood experiences differentially affect severity of PTSD, dissociative and depressive symptoms in adult inpatients. BMC Psychiatry 16, 295. https://doi.org/10.1186/s12888-016-1004-5.
Shapero, B.G., Black, S.K., Liu, R.T., Klugman, J., Bender, R.E., Abramson, L.Y., Alloy, L. B., 2014. Stressful life events and depression symptoms: the effect of childhood emotional abuse on stress reactivity. J. Clin. Psychol. 70, 209–223. https://doi.org/10.1002/jclp.22011.
Shionoya, K., Moriceau, S., Bradstock, P., Sullivan, R.M., 2007. Maternal attenuation of hypothalamic paraventricular nucleus norepinephrine switches avoidance learning to preference learning in preweanling rat pups. Horm. Behav. 52, 391–400. https://doi.org/10.1016/j.yhbeh.2007.06.004.
Sidamon-Eristoff, A.E., Cohodes, E.M., Gee, D.G., Peña, C.J., 2022. Trauma exposure and mental health outcomes among Central American and Mexican children held in immigration detention at the United States–Mexico border. Dev. Psychobiol. 64, e22227. https://doi.org/10.1002/dev.22227.
Starr, L.R., Stroud, C.B., Shaw, Z.A., Vrshek-Schallhorn, S., 2020. Stress sensitization to depression following childhood adversity: moderation by HPA axis and serotonergic multilocus profile scores. Dev. Psychopathol. 1–15. https://doi.org/10.1017/S0954579420000474.
Sullivan, 2001. Unique characteristics of neonatal classical conditioning: the role of the amygdala and locus coeruleus. Integr. Physiol. Behav. Sci. 36, 293–307.
Suri, D., Teixeira, C.M., Cagliostro, M.K.C., Mahadevia, D., Ansorge, M.S., 2015. Monoamine-sensitive developmental periods impacting adult emotional and cognitive behaviors. Neuropsychopharmacology 40, 88–112. https://doi.org/10.1038/npp.2014.231.
Sydnor, V.J., Larsen, B., Bassett, D.S., Alexander-Bloch, A., Fair, D.A., Liston, C., Mackey, A.P., Milham, M.P., Pines, A., Roalf, D.R., Seidlitz, J., Xu, T., Raznahan, A., Satterthwaite, T.D., 2021. Neurodevelopment of the association cortices: patterns, mechanisms, and implications for psychopathology. Neuron. https://doi.org/10.1016/j.neuron.2021.06.016.
Sydnor, V.J., Larsen, B., Seidlitz, J., Adebimpe, A., Alexander-Bloch, A.F., Bassett, D.S., Bertolero, M.A., Cieslak, M., Covitz, S., Fan, Y., Gur, R.E., Gur, R.C., Mackey, A.P., Moore, T.M., Roalf, D.R., Shinohara, R.T., Satterthwaite, T.D., 2023. Intrinsic activity development unfolds along a sensorimotor–association cortical axis in youth. Nat. Neurosci. 1–12. https://doi.org/10.1038/s41593-023-01282-y.
Wade, M., Zeanah, C.H., Fox, N.A., Tibu, F., Ciolan, L.E., Nelson, C.A., 2019. Stress sensitization among severely neglected children and protection by social enrichment. Nat. Commun. 10, 5771. https://doi.org/10.1038/s41467-019-13622-3.
Walker, C.-D., Sapolsky, R.M., Meaney, M.J., Vale, W.W., Rivier, C.L., 1986. Increased pituitary sensitivity to glucocorticoid feedback during the stress nonresponsive period in the neonatal rat. Endocrinology 119, 1816–1821. https://doi.org/10.1210/endo-119-4-1816.
Waters, R.C., Gould, E., 2022. Early life adversity and neuropsychiatric disease: differential outcomes and translational relevance of rodent models. Front. Syst. Neurosci. 16.
Webb, E.K., Carter, S.E., Ressler, K.J., Fani, N., Harnett, N.G., 2024. The neurophysiological consequences of racism-related stressors in Black Americans. Neurosci. Biobehav. Rev. 161, 105638. https://doi.org/10.1016/j.neubiorev.2024.105638.
Young, L.D., Suomi, S.S., Harlow, H.F., McKinney, W.T., 1973. Early stress and later response to separation in rhesus monkeys. Am. J. Psychiatr. 130, 400–405.
Yu, Q., Teixeira, C.M., Mahadevia, D., Huang, Y., Balsam, D., Mann, J.J., Gingrich, J.A., Ansorge, M.S., 2014. Dopamine and serotonin signaling during two sensitive developmental periods differentially impact adult aggressive and affective behaviors in mice. Mol. Psychiatr. 19, 688–698. https://doi.org/10.1016/j.avb.2008.06.003.

Zannas, A.S., Wiechmann, T., Gassen, N.C., Binder, E.B., 2016. Gene–stress–epigenetic regulation of FKBP5: clinical and translational implications. Neuropsychopharmacology 41, 261–274. https://doi.org/10.1038/npp.2015.235.

Zhang, Z.-Y., Mao, Y., Feng, X.-L., Zheng, N., Lü, L.-B., Ma, Y.-Y., Qin, D.-D., Hu, X.-T., 2016. Early adversity contributes to chronic stress induced depression-like behavior in adolescent male rhesus monkeys. Behav. Brain Res. 306, 154–159. https://doi.org/10.1016/j.bbr.2016.03.040.

Zhu, Y., Wang, M.-J., Crawford, K.M., Ramírez-Tapia, J.C., Lussier, A.A., Davis, K.A., de Leeuw, C., Takesian, A.E., Hensch, T.K., Smoller, J.W., Dunn, E.C., 2022. Sensitive period-regulating genetic pathways and exposure to adversity shape risk for depression. Neuropsychopharmacology 47, 497–506. https://doi.org/10.1038/s41386-021-01172-6.