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The effects of stress in early life and adolescence on posttraumatic stress disorder, depression, and anxiety symptomatology in adulthood

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Developmental windows of environmental sensitivity open and close throughout ontogeny, which can lead to vastly different effects of stress that depend upon age at exposure. It is well established that stress in adulthood can catalyze mental illness, but the effects of stress exposure during early life stages on the emergence and persistence of psychopathology remain unclear. Stress response systems undergo maturational changes that differ between early life and adolescence, and stress exposure during these two stages can have varying or even opposing consequences that persist into adulthood. In this review, we discuss clinical and rodent studies of developmental stages that seem to have distinct sensitivities to stress—early life and adolescence. We review the effects of stress during these two developmental periods on adult phenotype and risk for common stress-related disorders: depression, anxiety and posttraumatic stress disorder. We conclude by discussing challenges and recommendations for future research to investigate which features of developmental stress, or individual phenotype, may predict relative risk for common psychopathologies.

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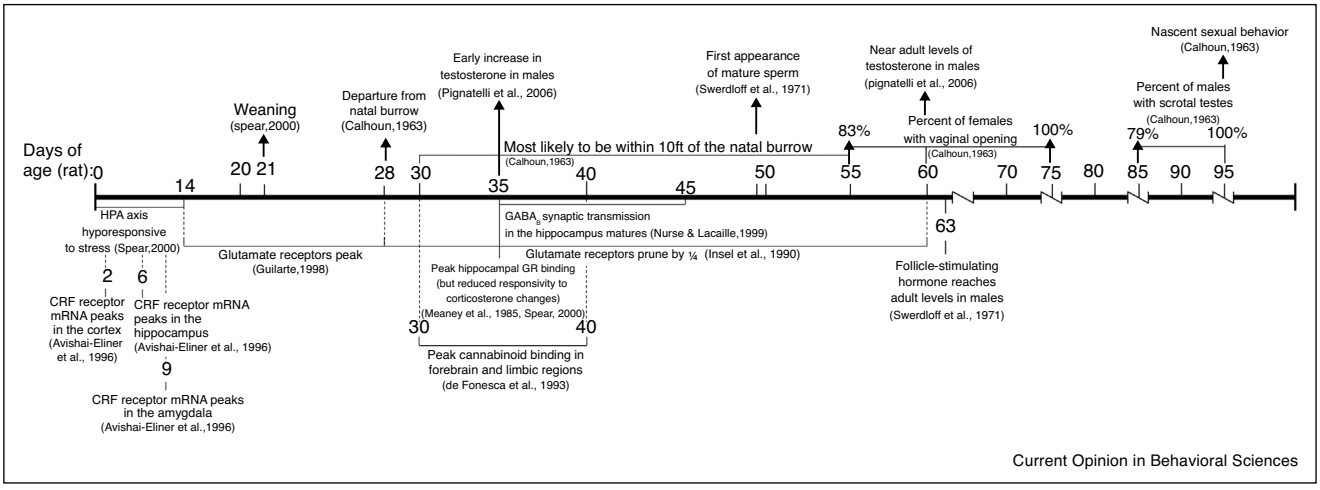
Introduction

Windows of sensitivity for developing systems open and close throughout ontogeny and stress can have vastly differing effects depending upon age at exposure. Decades of studies have demonstrated lasting effects of stress exposure before reproductive maturation on adult psychopathology ([1,77]). Among the various developmental periods the two key periods, early life (before weaning in mammals) and adolescence, share heightened phenotypic plasticity compared with other stages. Yet, studies show that stress exposure during these stages can have varying or even conflicting consequences [2] underscoring the importance of understanding the specific effects of stress exposure during both of these developmental periods. Both the nature and severity of consequences of stress exposure can be dependent upon age of exposure, for example, sexualized behavior occurs in nearly 80% of children sexually abused between 0–3 years of age, but this symptom drops nearly by half for children sexually abused between 13–17 years of age [3]. Conversely, recklessness can be linked to trauma during adolescence but not during early childhood ([78]). Similarly, with respect to hormonal stress axis function, retrospectively reported perceived stress between 0–5 years of age is correlated with increased CRF level in adulthood, whereas perceived stress between 6–13 years of age is correlated with decreased CRF levels in adulthood (in cerebrospinal fluid at rest; [4]). The impacts of stress in early life and adolescence may differ for at least three reasons: first, before weaning animals may produce less glucocorticoid "stress" hormone in response to aversive stimuli because of a period of hyporesponsivity to stress in early life maintained by the presence of the dam [5,2]. Yet, also in early life, CRF binding sites peak in rats at levels 300–600% higher than in adolescence (Figure 1, [6,7,79]). A second reason is that brain areas involved in stress regulation undergo distinct maturational processes in early life and adolescence in both rats and humans (outlined for rats in Figure 1). Finally, in humans, adolescents can perceive specific events as more stressful compared with children and adults [7].

Given that link between adult stress exposure and mental illness has been discussed extensively [8,9•], but the differential capacity for developmental stress at various stages to shape adult risk for psychopathology remains relatively underexplored, we focus here on two developmental stages that seem to have distinct vulnerabilities to stress, early life and adolescence. We discuss the relationship between the consequences of stress exposure during these two stages and symptomatology of common mental illnesses, depression, anxiety, and posttraumatic stress disorder, using clinical and rodent studies. To do this,

Figure 1



Timeline depicts developmental changes in behavior, physiology, and the brain, with an emphasis on early life and adolescence in rodents [69,70,71••,72,73••,74,75]. The age range denoted as adolescence varies across studies, but is generally between 28 to 42 days of age [7]. Given that a greater amount of data are available for male rats than for females, the timeline disproportionally represents male development. The Z breaks in the timeline at greater than 60 days of age illustrate that the timeline has been truncated.

we focus primarily on stress response systems, such as the hypothalamic-pituitary-adrenal (HPA) axis, and its product—glucocorticoid hormones, as their dysregulation has been extensively linked to disorders discussed here [2]. The review concludes with discussion of the characteristics of an early environment or phenotype that may affect the relative risk of specific pathologies and recommendations for future studies of the relationship between developmental stress and psychopathology.

Stress in early life can affect stress responses systems in adulthood

It is well established that exposure to stress in early life can alter responses to stress in adulthood [5]. During early life, neural and physiological systems regulating stress responses, including the hypothalamic-pituitary-axis, undergo maturation (Figure 1). Early maternal separation stress in rodents can have widespread lasting effects including exaggerated behavioral and hormonal responses to stress, increased CRF mRNA (in the periventricular nucleus, amygdala, and locus coeruleus), and increased CRF binding sites (in the amygdala, hypothalamus, hippocampus, and cerebellum) [10,11,2].

These effects of early maternal separation can generalize across species and some types of stress: voles exposed to social isolation in early in life exhibit increases in CRF mRNA in the hypothalamus in adulthood [12] and bonnet macaques reared by mothers exposed to unpredictable foraging demands also exhibit elevated CRF in adulthood [13]. Children separated from both parents during WWII can show enhanced cortisol responses to social stress in adulthood, and these effects are greater if parental separation occurred between 2–7 years of age than if separation occurred after seven years of age [14]. Despite similar findings across species, variation in stress type and within maternal separation procedures can contribute to variation in outcomes (reviewed in Lehmann and Feldon [15]. For example, exposure to a rodent model of early parental abuse, in which dams drag or throw neonatal pups, can decrease brain-derived neurotrophic factor (BDNF) mRNA expression in the hippocampus, amygdala, and prefrontal cortex [16,80]), while maternal separation can reduce BDNF mRNA expression in the hippocampus but not the prefrontal cortex ([81]). In humans, stress type can also shape lasting effects of early stress, for example, abused infants have a highly negative affect but neglected infants exhibit blunted affect ([82] Hiatt, 1984; [83]). These findings suggest that type of stress should be considered when generalizing and translating potential effects of early stress exposure.

While some effects of early stress are immediate, others only become apparent after additional stress exposure in adulthood. For example, maternally separated rats do not differ from unstressed rats in a forced swim test, but, if exposed to chronic restraint stress in adulthood, maternally separated rats show increased depressive-like behavior compared with rats reared without stress [17]. Similarly, maternal separation increases vulnerability to adverse effects of inescapable footshocks in adulthood in Wistar rats [18]. In addition to effects of early stress that are precipitated by subsequent stress, there are effects of early stress that can manifest after a delay, in the apparent absence of secondary stress, and may be triggered by developmental changes or environmental cues (termed

Predictive Adaptive Responses [19••]). It is suggested that effects of early stress may be delayed or triggered by secondary stress to allow organisms a wider range of possible phenotypes or to enable effects of stress to manifest during specific developmental stages [19••]. For example, environmental conditions in early life determine meadow vole coat thickness, which manifests after weaning and shapes winter preparedness [20]. Lasting effects of early stress, whether persistent or triggered by secondary stress, can increase anxiety-like and depressive behaviors in adulthood [21,22,17].

ELS and adult psychopathology

Epidemiological studies suggest that exposure to early life stress increases the risk of exposure to subsequent trauma in adulthood, and of anxiety, depression and posttraumatic stress disorder (PTSD) [23•,24••]. Early stress exposure can increase anxiety-like behavior in adult rodents across social, exploratory, and sexual contexts [21,25,22], but the relationship between anxiety-like behavior in rodents and human pathological anxiety is not straight forward. Converging evidence from clinical and animal studies suggests that early life stress can induce depression-like behavioral and neurological/physiological changes in stress response systems [24••]. For example, individuals with major depressive disorder can exhibit elevated basal glucocorticoids, increased CRF in cerebrospinal fluid ([84]), and blunted daily rhythms of cortisol ([85]). These effects have also been reported in adult rats exposed to maternal separation or low levels of maternal licking and grooming in early life ([22,26,27,28,86]). Maternal separation in rodents can also shape behaviors associated with depression in adulthood, including anhedonia in a sucrose preference test and behavioral despair in a forced swim test, though some report these effects only after secondary restraint stress in adulthood [21,29]. Further, the combined effects of maternal separation and secondary stress in adulthood can be attenuated by application of a selective serotonin reuptake inhibitor (SSRI) or environmental enrichment [21,11]. Although there is not a clear parallel for maternal separation stress in humans, infants given minimal physical and social stimulation in a Romanian orphanage also show elevated basal cortisol and disrupted daily rhythms of cortisol that can persist for years after adoption, and these effects are positively correlated with the duration of time in the orphanage [30]. Together these evidences may provide the strongest link between early life stress and vulnerability to a specific psychopathology in adulthood, depression.

There is, however, notable similarity between the lasting effects of early stress and some features of PTSD. For example, early stress in rodents can enhance startle responses and glucocorticoid receptor expression in adulthood (Lui et al., 1997; [22], and, following secondary stress as an adult, enhance fearfulness and anxiety-like behavior [31]. While a number of systems affected by early stress may contribute to an increased risk of psychopathology, effects across several systems have been linked to "programming" of the adult phenotype through epigenetic regulation of gene expression, such as DNA methylation of FKBP5, the BDNF gene, and the glucocorticoid receptor (GR) gene, NR3C1 [16,23•,73]. The latter, in turn, can affect negative feedback suppression of glucocorticoid production, which may increase vulnerability to lasting effects of trauma in adulthood. Decreases in basal cortisol and enhanced glucocorticoid negative feedback are often, but not always, found in PTSD patients, and some posit that this inconsistency might reflect lasting effects of exposure to early life stress in PTSD populations, rather than direct effects of trauma in adulthood [23•].

Similarly, studies of gene x environment interactions have generated evidence that interactions between genetic polymorphisms that affect neuron signaling (*e.g.*, serotoninergic and GABAergic cell functioning) and environmental features during development can either promote or protect individuals from developing internalizing disorders such as anxiety and depression (*e.g.*, early life stress and social support, respectively; [32]). For example, adults that express the 22/23EK variant of the NR3C1 gene and report exposure to stress during development (before age 18) are more likely to exhibit clinically relevant depressive symptoms, as well as decreased free cortisol [33,32]. However, in the absence of developmental stress this polymorphism conveyed no increased risk across any of the clinical/physiological features measured [33]. Another important gene x environment interaction is exemplified by heterozygous expression of the y2 subunit gene of the $GABA_A$ receptor, which causes deficits in GABAergic transmission and can increase anxiety-like behavior in adult mice as well as enhanced trace fear conditioning [34]. Deficits in GABAergic transmission are anxiogenic in humans and rodents; the y2 subunit is present in humans, but much is unknown about the functional significance of $GABA_A$ receptor subtypes in humans [35,36]. Further, $GABA_A$ receptors are reciprocally modulated by stress hormones, and maternal separation in rats can decrease GABA release in the adult hippocampus and enhance glucocorticoid levels [37]. In summary, accumulating evidence suggests that the effects of early stress exposure on adult psychopathology, particularly with respect to internalizing disorders, can be precipitated by genetic polymorphisms or unmasked by secondary stress in adulthood [21,22].

Stress in adolescence can affect stress responses systems in adulthood

Exposure to stress in adolescence can shape maturation of stress response systems and affect neurophysiological functioning in adulthood [38,39••]. Adverse experiences

during adolescence can also affect stress response systems in adulthood including basal, reactive, and circadian levels of glucocorticoids production, glucocorticoid and mineralocorticoid receptor expression in the hippocampus, and CRF levels, however the nature of these effects can vary greatly across studies. For example, stress responses can be enhanced [40–42], attenuated [40], or unaffected [42–44] following stress exposure in adolescence, with variations in stress treatments (*e.g.*, acute vs. chronic, repeated vs. unpredictable, social vs. physical vs. predation) or age at stress exposure, likely accounting for much of the variability in outcomes (reviewed in McCormick et al. [38,71]. Rodent studies of stress in adolescence span 21–84 days of age (which includes pre-puberty, puberty, and post-puberty, reviewed in Refs. [7,38,45••]). This wide range becomes especially salient when considering that one day of rat's postnatal life is suggested to be equivalent to one month for a human [46]. Variability in age range, animal species, and stress treatment can lead to conflicting findings as exemplified in the following studies: in the first, CD1 mice were exposed to social partner changes from 28–77 days of age, and no effect was found on CRF mRNA in the paraventricular nucleus of the hypothalamus (PVN) [47]. The second study exposed Long–Evans rats to social instability stress (partner change and isolation) from 30–45 days of age and found increased CRF mRNA in the PVN and reduced CRF responsivity to challenge [48]. To date, the effects of stress in adolescence on responsivity to stress in adulthood are still not well established, but a preponderance of studies show no lasting effects of stress in adolescence on HPA reactivity, suggesting that adolescence may be less susceptible to programming effects of stress on HPA axis reactivity compared with early life [38], though further studies are needed addressing other elements of the stress response systems.

Adolescent stress and adult psychopathology

The link between stress in adolescence and adult psychopathology has not been consistently demonstrated in epidemiologic studies. Early studies of natural disasters have reported that adolescents can be both more ([87]) and less vulnerable to trauma [49]. For example, two years after exposure to a dam collapse children showed greater PTSD symptomatology if they were exposed between the ages of 8–15 than if they were exposed between 2–7 years of age [49]. However, children exposed to an Australian bushfire, that were on average age at exposure, exhibited PTSD symptoms that were inversely correlated with age when measured 8 months after the fire, but positively correlated with both age and cumulative stress after 26 months [50].

Other studies suggest that the effects of adolescent stress on depressive and PTSD symptoms might be dose-dependent and vary between males and females [49]; Lonigan et al., 1994). In adolescents exposed to Hurricane Hugo, continued displacement was positively correlated with PTSD symptoms three months after the disaster (Lonigan et al., 1994), and in high school students depressive symptoms can be positively correlated with the quantity of past year adverse life in a dose-dependent fashion [51]. Similarly, it was reported that developmental exposure to stress between the ages of 0–18 can have dose-dependent effects on risk for depression in adulthood, but the relative effects of stress in early life and in adolescence are unclear (Chapman et al., 2004). Rodent models support a link between adolescent stress exposure and adult psychopathology, demonstrating that exposure to chronic stress in adolescence can cause cognitive and behavioral changes consistent with depression in adulthood, including a negative ambiguous judgment bias, increased response to reward devaluation [52], and, in some conditions, increased anhedonia (sucrose preference test) and behavioral despair, with strong effects of sex (reviewed in McCormick and Green [45••]. Complicating this, early life stress can increase drug and alcohol abuse in adolescence and adulthood, dependent upon sex and genotype, which can increase risk of subsequent trauma exposure and adversely affect trauma responses [53].

Sexes appear to differ in their susceptibility to lasting effects of stress in adolescence. In humans, adolescent females appear to be more reactive to stressors compared with adolescent males [54,55]. Similarly, in some animal studies, females exhibit lasting effects from stress while males appear unaffected; for example, exposure to chronic variable stress during adolescence decreases both sucrose consumption (suggesting anhedonia) and activity in a forced swim test in adulthood in female but not male rats [41,56]. Female rats are also more strongly affected by social defeat stress in adolescence; adult females that were exposed to social defeat in adolescence show increased anxiety-like behavior, including fewer approaches of a conspecific and increased time spent in closed arms in an elevated plus maze, compared with adult males with the same stress history [57]. These findings suggest that females may be more sensitive to lasting effects of stress in adolescence on anxiety and depressive behaviors in adulthood.

Lasting effects of stress during development on stress responsivity and risk of pathology

Although studies of stress in adolescence are accruing quickly, currently less is known about the lasting effects of adolescent stress on general stress reactivity and psychopathology compared with stress in early life. Decades of studies have shown that maternal separation in early life can enhance stress responsivity in adulthood, including HPA axis activity (reviewed in Refs. [5,11]. As we briefly reviewed above, the effects of stress in adolescence on stress responsivity in adulthood are less clear, but studies of stress in adolescence that vary in stress

type, length, and chronicity have found no lasting changes in HPA reactivity, suggesting that adolescence may be less susceptible to programming of HPA stress reactivity compared with early life [38]. Direct comparison of stress in early life and adolescence reveals both similarities and differences in HPA parameters linked to adult psychopathology. For example, both maternal separation and stress in adolescence have been linked to decreased glucocorticoid receptor (GR) mRNA in the hippocampus [5,47,38]. These effects are consistent with depression, which is marked by reduced GR function that can be reversed with SSRIs [58]. These findings further support the link between developmental stress exposure and depression. Conversely, increased CRF mRNA in the hypothalamus has been shown to result from early stress [5] but not stress in adolescence [47], and increases in CRF are associated with both depression and PTSD [27]. Distinct windows of development in GABAergic systems also appear to play a role in adult psychopathology; pharmaceutical potentiation of $GABA_A$ receptors before weaning can increase adult anxiety-like behavior in the elevated plus maze, yet the same treatment in adolescence (29–35 days of age in mice) increases depression-linked behavior but not anxiety-like behavior [59]. These findings suggest that age-specific consequences of stress exposure are linked to maturational windows, such as the peaking of CRF binding sites in early life which decline before adolescence (Figure 1).

It is important to note that the effects of stress in adolescence can be shaped by earlier exposure to stress, just as the effects of early stress can be modulated by prenatal stress [26,39••]. For example, recent evidence suggests that offspring of individuals with PTSD can have physiological hallmarks of PTSD in early life that may be linked to epigenetic effects including methylation of the NR3C1 gene promoter [60,61••]. This is consistent with evidence that suggests that the risk for specific psycopathologies can be shaped by genetic or environmental influences, for example, children exposed to stress between 0–18 years of age can develop depressive or anxious symptoms, and some of this variability can be explained by polymorphisms of the BDNF *Val66Met* gene [62] or socioeconomic status [63••]. While some suggest that children exposed to trauma have initially non-specific trauma responses that become more specific over time [64,65], it is also possible that more specific risks conveyed by developmental trauma are not yet understood, and may manifest after a delay because of links to ontogenetic changes such as puberty ([19]). For example, early life stress can affect cortisol-testosterone coupling between 11-15 years of age in girls, even though the role of testosterone is minimal in early life for women . Together these findings suggest that the effects of stress should be contextualized within an individual's history of stress [66] and, potentially, the stress history of their parents [60,61••], further, multiple outcomes of stress should be evaluated longitudinally and simultaneously.

Summary

The preponderance of evidence suggests that stress exposure in early life and adolescence can cause lasting effects on stress responsivity systems, though some systems may be more vulnerable in early life than in adolescence. For example, early maternal separation is associated with increased CRF signaling and binge alcohol consumption [67••], while stress in adolescence links to increased alcohol consumption only in individuals with the C-allele of CRF receptor 1, and otherwise has minimal effect on CRF signaling [38,68]. This also suggests that individual variation may have a greater role in determining the consequences of stress in adolescence than in early life.

Epidemiologically, developmental stress can contribute to numerous pathologies. The pathological specificity of stress in development is largely unknown, though some of the strongest evidence supports a link with depression [62,38].

There is strong evidence of a link between PTSD-like symptomatology and traumatic experiences in early life and adolescence [50,49,61••], but these effects generally manifest quickly after trauma and may involve different mechanisms than those implicated in the lasting effects of stress in early life and adolescence on depression. More research is required to address the potential link between developmental stress and subsequent risk for posttraumatic psychopathology.

Overall, more comprehensive studies are required to address many remaining questions. The existing literature suggests that studying the effects of childhood trauma without examining subgroups between 0–18 years of age might not be informative enough, as stress in early life and adolescence can lead to opposing findings [4,2]. Further, consideration of history of stress exposure (parental, *in utero*, early childhood) might be required to fully ascertain the potential contributions of environmental and epigenetic variables. Similarly, comprehensive examination of potential outcomes (depressive, anxiety, PTSD, substance use) will be required both in epidemiologic and mechanistic (animal model) studies to address issues of pathological specificity of developmental risks.

Conflict of interest statement

The authors declare that they have no conflicts of interest to report.

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