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Psychobiological mechanisms underlying the association between early life stress and depression in adolescence

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Early life stress (ELS), or exposure to adverse experiences before the age of 18 years, is alarmingly prevalent and is a strong risk factor for the development of depression in adolescence. Despite the consistency of this association, we do not fully understand how, or for whom, ELS gets 'under the skin' to increase adolescents' risk for experiencing depression. In this context, researchers have identified psychobiological characteristics that may serve to link early adversity to risk for adolescent depression. In this paper we discuss four of these characteristics: stress reactivity, reward processing, inflammation, and biological aging. For each of these putative mechanisms we describe the nature of their associations with both ELS and depression, focusing when possible on these relations during adolescence. In addition to being a vulnerable period for the emergence of depression, adolescence is also characterized by developmental shifts in critical domains of psychobiological functioning that add nuance to the associations with early life stress and depression. Following this presentation, we discuss how these constructs likely co-occur and interact in ways that alter the relation between early adversity and risk for adolescent depression; we also consider factors that might serve to moderate this association. We conclude by describing unresolved issues and suggesting directions for future research concerning the ways that ELS increases adolescents' risk for the development of depression. Specifically, we discuss how researchers might address the lack of consistency in findings examining associations among ELS, biological functioning, and depression in adolescent samples by examining systematically the types of stress experienced, the biological functioning and specific aspects of depression that are assessed in each study, and moderators such as participants' sex, developmental stage, and family history. We seek to stimulate researchers to examine other mechanisms that might underlie the association of early adversity with depression in order to inform the development of more effective approaches to the prevention and treatment of this debilitating disorder.

Molecular Psychiatry; https://doi.org/10.1038/s41380-025-03348-8

Early life stress (ELS) is often defined as exposure to adverse experiences occurring before the age of 18, including physical and emotional abuse and neglect, sexual abuse, material deprivation, and neighborhood violence [1]. ELS is alarmingly prevalent and is a leading risk factor for the development of psychopathology and, in particular, depression [2]. Although ELS has been found to adversely affect health through adulthood [3, 4], its effects are particularly pernicious during adolescence, when brain and biology are developing rapidly in the context of a quickly evolving social landscape and the prevalence of depression begins to peak.

Despite the consistent association of ELS with depression, we do not yet have a comprehensive understanding of how, or for whom, early adversity gets 'under the skin' to increase adolescents' risk for experiencing this disorder. Indeed, the considerable variability in the development and course of depression following exposure to ELS suggests both that some individuals are resilient to the effects of early adversity and that there are important differences in the nature of the association of particular types of ELS with risk for depression.

Over the past decade researchers have identified several biological characteristics that may function as mechanisms linking early adversity to risk for depression in adolescence. These characteristics operate across many levels throughout the body, extending from stress-related hormones, to large-scale brain circuits, to inflammatory functioning, to increased mitochondrial DNA (mtDNA) copy number and telomere shortening. Considered collectively, these characteristics reflect the operation of four broad constructs: *stress reactivity*, *reward processing*, *inflammation*, and *biological aging*. Importantly, each of these constructs and related characteristics have been associated with both early adversity and depression, supporting the formulation that they serve as mechanisms through which ELS is linked to the subsequent development of depression.

In this paper we discuss how each of these four constructs might mediate the relation between exposure to ELS and risk for depression in adolescence. We begin by describing the conceptualization and measurement of early adversity, including recent efforts to distinguish among various types of early experiences and environments to which adolescents may be exposed. Next, we describe the high prevalence of depression in adolescence and the implications of this early onset for the course of this disorder. We then present findings of studies linking early exposure to stress or adversity with risk for depression in adolescents. Next, we discuss biological characteristics that may

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Received: 19 June 2025 Revised: 10 October 2025 Accepted: 6 November 2025
Published online: 16 November 2025

function as mechanisms that connect stress exposure to risk for depression. In this context, we focus on stress reactivity, reward processing, inflammation, and biological aging, as well as each of their associations with both early adversity and depression. We then discuss how these constructs likely co-occur and interact in ways that alter the relations between early adversity and risk for depression in adolescents in the context of other possible moderators, such as family-genetic risk. Finally, we raise unresolved issues and suggest directions for future research that we believe will advance our understanding of how ELS increases adolescents' risk for the development of depression.

EARLY ADVERSITY

Researchers have estimated that more than half of individuals have been exposed to at least one form of ELS [5, 6]. Importantly, exposure to early adversity has been associated with elevated rates of mental health difficulties across the lifespan and, in particular, with the development of depression (e.g., [7]. LeMoult et al. [8] found that some forms of adversity (e.g., emotional abuse) are more strongly associated with emotional difficulties than are other stressful experiences (e.g., economic adversity). Indeed, there is now a sizable body of research examining differential effects of various types of ELS on individuals' health.

In this context, investigators have attempted to characterize stressor-outcome relations by constructing taxonomies of early stress that distinguish different types, or dimensions, of adversity, each with presumed specific biological or behavioral sequelae. For example, Ellis et al. [9] focused on aspects of the environment that are particularly harsh and thereby pose a threat to individuals' wellbeing (e.g., abuse, violence), and on the extent to which harshness is predictable or unpredictable. From this perspective, exposure to harshness leads to faster development in the service of prioritizing growth before an individual experiences more harm [10]. This accelerated development is particularly pronounced if the harshness is unpredictable, which signals that resources should be allocated to the present given the uncertainty of the future [9]. Ellis et al. [10] hypothesized that, in contrast, deprivation of psychosocial and material resources (e.g., neglect, poverty) leads to delayed development.

A different approach to distinguishing among types of early adversity was proposed by McLaughlin, Sheridan, and Lambert [11], who differentiated ELS characterized by threat from adversity characterized by deprivation. Like Ellis et al.'s [9] focus on harshness, McLaughlin et al. postulated that threat signals risk to an individual's wellbeing. They posited that early exposure to threatening experiences not only activates neural circuits underlying aversive learning and salience detection but also sensitizes these circuits to future potentially threatening stimuli, ultimately manifesting as psychopathology. Sheridan and McLaughlin [12] posited that, in contrast, deprivation of material or psychosocial resources leads to a lack of expected input required for typical neural development, which, in turn, may lead to deficits in neural development and, consequently, in cognitive functioning. Supporting these formulations, MacSweeney et al. [13] recently found that more threatening or traumatic early experiences in female youth were associated with higher levels of internalizing symptoms.

Despite the importance of these proposed distinctions, in reality adverse experiences are multifaceted and often co-occur. Thus, investigators are increasingly attempting to use data-driven approaches to delineate meaningfully distinct experiences of ELS that may have unique effects on biological and development outcomes (e.g., [14, 15]. Further, researchers must also be cognizant that how adverse experiences are assessed can affect their findings. For example, different results may be obtained when ELS is measured prospectively versus retrospectively (e.g., [16, 17], subjectively versus objectively (e.g. [18–20], and by participant versus other informant [20].

DEPRESSION IN ADOLESCENCE

Adolescence is a period of rapid physical, emotional, and cognitive change, and of heightened emotional reactivity [21]. It is also the most sensitive developmental period for the onset of affective disorders like depression. Indeed, recent epidemiological data indicate that as many as 25% of adolescents ages 12-17 years – and nearly 1 in 3 girls – will experience at least one episode of Major Depressive Disorder (MDD), which commonly peaks in adolescence [22, 23]. Importantly, adolescent-onset MDD adversely affects the course and prognosis of MDD. Almost half of depressed adolescents have recurrent episodes within three years of onset [24]; further, early-onset MDD is associated with longer depressive episodes that are often refractory to treatment [25] and with functional impairment that increases their risk for longstanding difficulties [26].

EARLY ADVERSITY AND DEPRESSION

Researchers have provided compelling evidence that exposure to ELS is associated with significant increases in the risk for the development of psychopathology over the life course [8, 27]; in fact, adverse experiences in childhood are stronger predictors of psychopathology than are similar experiences later in life [28, 29]. In particular, depression is a frequently documented consequence of ELS; indeed, the most common environmental antecedent of depression is exposure to stressors [30]. Further, depression is more likely to be comorbid with other disorders [31] and more resistant to treatment in individuals who have experienced ELS than in persons with no history of significant early adversity [32]. Finally, ELS has been found to be associated with a 2- to 5-fold increase in risk for attempted suicide [33], a leading cause of death in people ages 10-24. Given these alarming statistics, combined with the fact that over 6 million cases of maltreatment are filed in the US each year [34], it is critical that we elucidate the mechanisms through which ELS increases individuals' risk for depression; doing so will inform the development of more effective approaches to the prevention and treatment of this debilitating disorder.

MECHANISMS LINKING EARLY ADVERSITY WITH DEPRESSION IN ADOLESCENCE

Although it is clear that ELS is associated with the development of depression, we do not yet understand the *mechanisms* by which ELS leads to depression. Only recently have researchers begun to formulate and test theoretical models regarding mechanisms that link ELS to risk for depression (e.g., [35]). In the following sections we describe biological processes that may each function as a mechanism that connects stress exposure to risk for depression; specifically, we consider stress reactivity, reward processing, inflammation, and biological aging, and describe their associations with both early adversity and depression.

ELS AND STRESS REACTIVITY

Researchers have increasingly examined the role of sensitivity or reactivity to acute stressors in the development of depressive symptoms and diagnoses. From a theoretical perspective, investigators have posited that experiences of stressors occurring early in life are particularly impactful by increasing individuals' sensitivity to stress later in development. The stress sensitization model, which builds on Post's kindling hypothesis [36], predicts that exposure to adverse events, especially those occurring early in life, "primes" individuals to be more sensitive and reactive to

and, therefore, affected more strongly by, later stressful experiences [37]. Researchers have postulated that this increasing stress sensitivity and accompanying stress reactivity over time contributes to the onset of psychopathology, particularly depression [38, 39].

Stress reactivity, generally defined as the body's response to a stressor (e.g.,[40, 41]), has been operationalized using different biological systems, which may help to explain the inconsistent findings reported in the literature. For example, whereas Duprey et al. [42], Peckins et al. [43], and Wade et al. [44] found that early abuse and severe deprivation are associated with hypo-reactivity of the parasympathetic nervous system (PNS), the sympathetic nervous system (SNS), and the HPA axis, these findings were not replicated by Bönke et al. [45], Buthmann et al. [46], or Schuurmans et al. [47]. In fact, some of these studies found hyper-reactivity of these systems, raising questions about the validity of stress reactivity as a unitary construct [48]. Raising further concerns, Brindle et al. [49] conducted a meta-analysis and found that the associations between ELS exposure and both cardiac and cortisol reactivity were small and negative. It is clear that additional research is required to gain a more comprehensive understanding of the nature of the associations between different kinds of ELS and modality-specific stress reactivity.

Altered reactivity to stressors is particularly relevant in adolescence, when individuals undergo dramatic puberty-related neuroendocrine changes. Increases in gonadal hormones and in progesterone secreted from the hypothalamic-adrenal-gonadal (HPG) axis, as well as functional alterations in the hypothalamus, have been found to be associated with different patterns of stress reactivity in adolescents than in children and adults [50]. In addition, the brain undergoes structural and functional changes during puberty in areas that underlie emotion regulation [51, 52]. Importantly, these alterations have been found to occur earlier in individuals who have experienced ELS [27]. DePasquale et al. [53] and Gunnar et al. [54] have reported similar alterations in the normative trajectory of cortisol reactivity across adolescence in youth who were raised in institutional care. It is not yet clear, however, whether similar patterns of altered stress reactivity also characterize adolescents exposed to threat-related ELS.

STRESS REACTIVITY AND DEPRESSION

As with the relation between ELS and stress reactivity, the association between stress reactivity and depression also appears to be multifaceted. For example, several investigators have examined reactivity in heart rate variability (HRV), which reflects phasic modulation of the parasympathetic nervous system. Whereas some researchers have found this measure to be blunted in depression [55], others have found HRV to be potentiated in this disorder (see [56]. The tasks used to assess stress reactivity may contribute to these discrepant findings. For instance, Hu et al. [57] reported that in adults with depression and anxiety, heart rate and RSA reactivity were blunted during a cognitively demanding task (i.e., n-back) but elevated during a psychiatric interview.

Investigators have also assessed the relation between HPA-axis functioning and depression; this literature, too, has yielded mixed findings. While HPA-axis function can be assessed using many measures and techniques, many studies rely on measures of cortisol reactivity, which has generated a particularly rich literature. Whereas Duprey et al. [42] linked blunted cortisol reactivity with higher internalizing symptoms, Perry et al. [58] found that higher cortisol reactivity was associated with greater depressive symptomatology in adolescents who experienced deprivation. Biological sex may explain some of the discrepant findings: for example, Zorn et al. [59] found that whereas depressed females had blunted cortisol reactivity, depressed males had increased reactivity. It is clear that more research is required to gain a better understanding of the nature of the relation between stress reactivity and depression, particularly in youth.

STRESS REACTIVITY AS A MECHANISM LINKING ELS WITH DEPRESSION

Stress reactivity can be assessed with various measures that are often only weakly intercorrelated. Different studies have used different measures, which, as was the case with the findings we described above concerning the relation between ELS and stress hypo- versus hyper-reactivity, has led to inconsistencies in the literature. There is some evidence across diverse measures that high stress reactivity following exposure to ELS increases individuals' risk for developing depression and other forms of psychopathology [60]. For example, several researchers have found that higher stress reactivity moderates the association between stressful conditions and psychopathology across modalities [61], including reactivity assessed through self-report measures [62], measures of cardiac PNS function [63], measures of skin conductance as it relates to SNS [64, 65], and HPA-axis function indexed by cortisol [66]. Here, too, however, some investigators have found that hypo-reactivity of the PNS [67] and HPA axis [44] confers greater risk for both depression and externalizing symptoms in individuals who have experienced ELS [44].

Assessing brain functioning, Yamamoto et al. [68] found in a small sample of adults that heightened amygdala reactivity to a negative mood induction task attenuated the association between ELS and depressive symptoms, suggesting a potential buffering role for stress reactivity. Longitudinal research with larger samples is needed to elucidate whether and under what conditions stress reactivity potentiates or attenuates the adverse effects of early adversity on the development of depression. Assessing the types of ELS experienced, the specific form or modality of reactivity assessed, and the age and sex of participants will be important in disentangling these different effects.

ELS AND REWARD PROCESSING

Adolescence is characterized by significant development in brain regions and circuits involved in motivation and reward processing. Such circuits encompass widely distributed areas of the brain, including the ventral striatum (VS)/nucleus accumbens (NAcc), ventral tegmental area (VTA), and various expanses of prefrontal cortex (PFC) (e.g., medial PFC, orbitofrontal cortex). This development includes such changes as heightened VS activation to reward during adolescence relative to childhood and adulthood [69, 70], and continued, protracted development of regulatory PFC regions and frontostriatal connections [71, 72]. These changes in mesolimbic and frontostriatial circuitry over adolescence – and the relative imbalance between the reward and regulatory systems – are posited to underlie the increase in exploration, social motivation, and reward-seeking behaviors (i.e., risk taking) typically observed during adolescence [71, 73] that is critical for facilitating self-regulation, goal-directed behaviors, and cultivation of meaningful social relationships [74].

A considerable body of research has linked ELS to alterations in reward-related neural circuitry during adolescence [28, 75], including weaker frontostriatal white matter tract integrity [76], altered VS volume [77], stronger resting frontostriatal connectivity [78], and altered activation during reward processing [79]. Further, there is also evidence of differential associations by types of ELS [77, 80]. Thus, there is little consensus about precisely *how* ELS is associated with altered reward-related neural circuitry during adolescence – likely due to variability in types of ELS, imaging modality, behavior assessed, and population characteristics – although we should note that there is relatively consistent evidence that ELS affects mesocortioclimbic circuitry [81].

REWARD PROCESSING AND DEPRESSION

Alterations in reward processing have long been associated with core symptoms of depression, including anhedonia, low motivation, and psychomotor retardation [82]. Some studies have found aberrant functioning of reward circuitry to precede the onset of depression in adolescence [83, 84]. In contrast, other research has found evidence of bidirectional influences between depressive symptoms and reward-related neural activation during this developmental period. For example, Rappaport et al. [85] assessed a sample of youth annually from ages 3-5 years into adolescence and found that whereas *current* severity of depression was associated with blunted NAcc response to reward anticipation, *cumulative* severity of depression across development was associated with more widespread blunting across the corticostriatal circuit. These findings suggest that there are important distinctions between alterations in neural reward circuitry that are associated with a history of depression and those related to current levels of depression.

REWARD PROCESSING AS A MECHANISM LINKING ELS AND DEPRESSION

Several studies have linked ELS-related alterations in reward circuitry to higher levels of internalizing symptoms. For example, Hanson et al. [86] found that individuals exposed to greater levels of emotional neglect had a blunted developmental increase in VS activity, which in turn was related to higher depressive symptoms. There is also evidence that ELS interacts with reward circuitry to predict internalizing symptoms. For instance, using data from the ABCD study, Yang et al. [87] found that, for youth with low family conflict, greater VS activity during reward receipt at baseline predicted fewer internalizing symptoms a year later; in contrast, youth from high-conflict families had higher levels of internalizing symptoms regardless of their reward sensitivity.

ELS AND INFLAMMATION

Inflammation may operate as a mechanism that links exposure to childhood adversity and disease. Chronic stress may alter immune regulation, leading to chronic inflammation [88, 89]. In turn, as we describe in more detail below, elevated levels of inflammation have been implicated in the development of depression. A number of researchers have documented associations between experiences of adversity in childhood and inflammation in adulthood [90, 91]. For example, in a large longitudinal study, Danese et al. [92] found that cumulative exposure to childhood maltreatment related to higher inflammation 20 years later. Indeed, a meta-analysis of studies examining the relation between childhood trauma exposure and inflammatory markers in adulthood yielded significant, if small, effect sizes [90].

Less research, however, has been conducted in youth samples. Danese et al. [93], Slopen et al. [94], and Copeland et al. [95] all reported that early exposure to adversity was associated with higher levels of inflammatory markers in childhood. Similarly, Chiang et al. [96] documented that the association between ELS and inflammation strengthens through adolescence and early adulthood. In a recent meta-analysis of studies of inflammation in youth exposed to ELS, however, Kuhlman et al. [97] reported that the associations between early adversity and both CRP and IL-6 were small. It is clear, therefore, that more research is needed examining the nature of the association between early adversity and inflammation in youth.

INFLAMMATION AND DEPRESSION

High levels of inflammation may contribute to stress-related psychiatric conditions such as depression and anxiety [98, 99]. To date, most studies examining associations between inflammation and depression have focused on adults (e.g., [100, 101]. In meta-analyses of studies of inflammation and depression in adults, Köhler et al. [102] and Osimo et al. [103] found significant associations between depression and cytokines. However, the directional nature of the association between depression and inflammation remains unclear. Whereas some studies have reported that depression leads to subsequent inflammation [104, 105], others have found the reverse association, with concentrations of inflammatory markers predicting depressive symptoms [106, 107]. In a recent meta-analysis Colasanto et al. [108] reported both significant concurrent and bidirectional associations between depression and CRP and IL-6.

Investigators examining samples of youth have reported similar, if somewhat weaker, correlations between inflammation and depression. Ferencova et al. [109] found that adolescents diagnosed with MDD had higher levels of cytokines than did nondepressed controls. Toenders et al. [110] reviewed a number of studies examining the association between inflammation and depression in youth and found what they referred to as "subtle evidence" for inflammatory dysregulation in youth depression, with some evidence of a bidirectional association between inflammation and depression in youth.

INFLAMMATION AS A MECHANISM LINKING ELS WITH DEPRESSION

Given findings that inflammation is associated with both ELS and depression, researchers have posited that inflammation mediates this relation. For example, Danese et al. [111] found that early adversity characterized by maltreatment and deprivation was associated with both inflammation and depressive symptoms in adulthood. Similarly, Miller and Cole [112] found that adolescents who both experienced ELS and reported higher levels of depressive symptoms had greater increases in both IL-6 and CRP than did matched controls. In contrast, however, in a study of almost 4000 youth, Iob et al. [113] examined the longitudinal associations of experiences of early adversity with inflammation in adolescence and trajectories of depressive symptoms through young adulthood. Iob et al. found that while most types of early adversity were associated with elevated trajectories of depressive symptoms, inflammation did not mediate these associations of adversity and depression, suggesting that associations of early adversity with depression in youth are only weakly, if at all, mediated by inflammation.

ELS AND BIOLOGICAL AGING

Beyond the factors reviewed above, ELS may also alter the pace of development in ways that vary both with the type of ELS experienced and with the biological systems being examined. As noted above, early experiences may program an individual to respond more effectively to anticipated demands [10]. In this context, difficult environments may speed development in ways that facilitate reproduction [10, 114]. In fact, in a meta-analysis focused on adolescents, Colich et al. [115] found that ELS characterized by threat was associated with accelerated pubertal development.

Alterations in early development may have parallels with measures of cellular aging. The Predictive Adaptive Response (PAR) hypothesis posits that there are internal and external PAR advantages of accelerated reproduction [116]: whereas external PAR predicts the kind of environment into which the child will mature, internal PAR predicts the future state of the child's body. If the body anticipates a shortened cellular life span, due perhaps to threat-related ELS, the adaptive evolutionary response is to accelerate biological aging, increasing the likelihood of reproduction. Early experiences of threat have been associated with accelerated cellular aging, characterized by shorter telomere

length, higher mtDNA copy number, and advanced epigenetic age [115, 117]. Importantly, conceptually similar findings have been reported concerning threat-related acceleration of trajectories of the development of brain regions involved in emotion processing, associative learning, and memory, including the amygdala, hippocampus, and fronto-amygdala connectivity [118].

BIOLOGICAL AGING AND DEPRESSION

Although accelerated biological aging and brain development in the context of ELS may facilitate reproductive success or individual survival, it is important to remain cognizant of the considerable evidence of the long-term costs of stress exposure. Indeed, both accelerated pubertal timing [119, 120] and accelerated cellular aging [121, 122] have been linked to a range of physical and mental health problems, including depression. For example, Hamlat et al. [123] demonstrated that self-reported early pubertal timing predicted the onset of the first depressive episode in youth as well as length of the interval between depressive episodes. Further, Humphreys et al. [124] reported that depressive symptoms preceded accelerated cellular aging during adolescence, which might help to explain the comorbidity of depression with physical health problems. Finally, researchers assessing "brain age" (i.e., the discrepancy between individuals' chronological age and their predicted brain age) have found that depressed adolescents have older looking brains than do healthy controls (e.g., [125], particularly with respect to accelerated frontal lobe cortical thinning [126], accelerated development of striatal connectivity with subgenual cingulate, hippocampus, and amygdala connectivity, and delayed intra-striatal connections [127].

BIOLOGICAL AGING AS A MECHANISM LINKING ELS AND DEPRESSION

As reviewed above, distinct literatures have found separate associations among ELS, indices of biological aging, and depressive symptoms. Nevertheless, few studies have examined relations among these constructs in the same individuals. The small number of studies that have done so have yielded inconsistent findings. For example, Rampersaud et al. [128] found that whereas experiences of childhood abuse were associated with epigenetic age acceleration in adults with depression, childhood household dysfunction was associated with decelerated epigenetic age. In adolescents, greater exposure to threat-related ELS has been associated with earlier age of menarche in girls, which in turn was associated with post-menarche onset of distress [129]. However, in a subsequent study, Colich et al. [130] found that threat-related ELS was not associated with pubertal timing in girls, but was in boys, which in turn was related to greater externalizing problems. Finally, MacSweeney et al. [13] found in female youth that more threatening early experiences were associated with earlier pubertal maturation, which in turn mediated the association between threat-related ELS and internalizing symptoms.

Some of these inconsistencies could reflect between-study differences in measurement. For example, although pubertal development involves a range of distinct yet intercorrelated processes such as adrenarche, gonadarche, and menarche that may have unique effects on brain development and behavior (e.g., [131], researchers commonly use only a single score to represent pubertal stage that aggregates these processes. Variation in assessments represents another source of inconsistency (e.g., through self-report or hormone concentrations). While the measurement and analyses of pubertal development are not without challenges [132], multimodal assessments of puberty are needed [133] to elucidate how pubertal timing might mediate the link between ELS and risk for depression in adolescence.

Mixed findings have also been reported concerning brain maturation and depression. For example, whereas J. Miller et al. [134] found that greater neighborhood socioeconomic disadvantage was associated with a thinner cortex (suggesting accelerated maturation) that, in turn, was associated with more depressive symptoms, Cohen et al. [135] found that adolescents from lower SES households exhibited lower brain age (suggesting delayed maturation) that was associated with higher anxious/depressed scores. Thus, although there are promising findings in initial studies linking early adversity, biological aging, and depression, it is difficult to draw strong conclusions from inconsistent findings obtained from relatively small samples.

INTERACTIONS OF MECHANISMS

In the preceding sections we have documented associations of stress reactivity, reward processing, inflammation, and biological aging with both early adversity and depression. We have also described the results of studies examining how each of these factors might link ELS to risk for depression. Although we have discussed these four putative mechanisms separately, we contend that they are best considered together, as co-occurring, interacting factors that alter the relation between early adversity and risk for depression in adolescence. In fact, several researchers have begun to examine interactions among these variables, albeit not yet in the context of the relation between ELS and depression in youth.

Perhaps the strongest theoretical foundation for examining the interaction of mechanisms that might link early adversity with depression is the neuroimmune network hypothesis [136, 137], which proposes that exposure to ELS amplifies the normative bidirectional communication between the brain and the immune system. Consistent with this formulation, in both experimental and observational studies researchers have found that higher inflammation is related to greater amygdala activation to negative stimuli [138, 139]. In a more complex test of the neuroimmune hypothesis, Miller [140] reported that early adversity interacts with amygdala reactivity during threat-processing to predict a proinflammatory phenotype in early adolescence. This finding was extended recently by Yuan et al. [141], who reported that adolescents who experienced greater early adversity exhibited increases in inflammation that were associated with reductions in amygdala gray matter volume, suggesting accelerated biological aging.

Researchers have found that inflammation is also related to altered reward processing. For example, Yuan et al. [142] demonstrated that higher levels of CRP were associated with blunted NAcc activation during the processing of monetary rewards in youth with greater exposure to ELS, and [143] found that higher IL-6 was associated with greater NAcc activation in adolescents who lived in neighborhoods with more crime. Similar findings have been reported by researchers examining interactions between neural activation and HPA-axis reactivity. For example, LeMoult et al. [144] reported that greater VS activation to the anticipation of reward is associated with higher cortisol levels in adolescent girls. In a longitudinal study, Vidal-Ribas et al. [145] found that blunted activation of reward circuitry at age 10 predicted higher stress-related cortisol reactivity three years later. Finally, in the context of reporting that ELS is associated with stronger negative frontoamygdala connectivity during emotion processing in early adolescence, J. Miller et al. [146] found that this connectivity in turn was associated with slower telomere shortening and slower pubertal tempo over a two-year period, suggesting that ELS-related acceleration of frontoamygdala circuitry protects against accelerated biological aging. By examining interactions among multiple biological mechanisms, studies such as these have the potential to advance our knowledge of

precisely how early adversity alters biological functioning to increase risk for depression in adolescence.

A related issue involves a consideration of genetics and, more specifically, a family history of psychiatric disorders as a factor that may moderate the relation between early adversity and depression in youth. In this context, researchers have documented genetic influences on both childhood adversity (e.g., [147, 148]) and depression (e.g., [149, 150]). Further, Chen et al. [151] recently conducted Mendelian randomization analyses on data from the UK Biobank and found that childhood maltreatment was genetically correlated with risk for depression in adulthood, highlighting the enduring adverse consequences of childhood adversity for mental health. Importantly, the intergenerational transmission of risk for depression has been found to be attenuated by an intervention that targets parenting and children's interpersonal, intrapersonal and academic skills, which Gorla et al. [152] documented disrupts the pathways from parents' depressive symptoms to their grandchildren's emotional difficulties through lowering their children's depressive symptoms.

It is noteworthy that the inclination to appraise or recall certain childhood experiences as victimization has also been found to be genetically influenced [148, 153], which may contribute to the discrepancies between self- vs. informant-reported, and between prospective vs. retrospective reports of, early adversity. And adding a further complication, the psychobiological characteristics we discussed above as possible mechanisms through which childhood adversity affects depression in adolescence have themselves been found to be genetically influenced (e.g., [154–156]). Thus, it will be important in future studies that investigators systematically consider the role of genetics in understanding the nature of associations among ELS, psychobiological functioning, and adolescent depression.

UNRESOLVED ISSUES AND DIRECTIONS FOR FUTURE RESEARCH

In this paper we discussed the link between ELS and adolescent depression and presented research examining how each of four constructs – stress reactivity, reward processing, inflammation, and biological aging – may function as mechanisms that underlie this association. Despite our progress in understanding the nature of the relation between early adversity and depression in adolescence, a number of questions remain unresolved. In this final section of the paper, we present issues that we believe researchers must address if we are to advance our understanding of how stress gets under the skin to increase adolescents' risk for depression.

One theme that emerges throughout this review concerns the lack of consistency in findings examining the associations among ELS, biological functioning, and depression, particularly in adolescent samples. For example, whereas some researchers have reported that high levels of stress reactivity moderate the association between ELS and risk for depression (e.g., [61], others have found that hypo-reactivity confers greater risk (e.g., [67]. Similarly, whereas Colich et al. [129] found that greater exposure to ELS was associated with earlier age of menarche in girls, Colich et al. [130] reported that early adversity was associated with pubertal timing in boys, but not in girls. Such inconsistencies are likely due to several factors, including the type of stress experienced, the biological functioning assessed, and the sex and developmental stage of the participants. Further, as we suggested above, there are likely additive and/or compensatory interactions among these biological systems that modulate this risk. If we are to make meaningful progress in understanding how early adversity influences risk for depression, it is critical that we examine these factors as systematically as possible.

In this context, researchers should attempt to replicate findings using the same modality of assessment (e.g., self-report, cortisol reactivity, frontostriatal connectivity) and task (e.g., Trier Social Stress Test, Monetary Incentive Delay task); such replications are essential in moving the field forward, as are meta-analyses when enough relevant studies have been published. It is also imperative that researchers systematically examine the moderating effects of age and pubertal status in the association of ELS with depression. For example, puberty-related changes in brain structure and function have been linked to alterations in both stress reactivity [51, 54] and reward processing [70]. Studies in which results are averaged across adolescent males and females with wide age ranges are likely to obscure important sex- and maturation-specific findings that would help to elucidate biological mechanisms involved in the development of depression in youth following ELS.

Future studies would also benefit from assessing multiple domains of biological functioning that might link early adversity and depression within a single sample (e.g., [61]. Generating more precise profiles of psychobiological functioning following ELS may elucidate both different paths to the development of depression and promising targets for intervention. In addition, obtaining longitudinal data from a single sample of participants as they age and move through puberty will advance our understanding of the rapid shifts in psychobiological functioning during this period, particularly with respect to the effects of early adversity on the development of depression. Although these goals of expanding both the breadth and depth of assessments will require innovative approaches that minimize participant burden and habituation effects, findings from such studies will be critical in elucidating the nature of the association of ELS and depression in adolescents.

As a related point, as the conceptual and methodological complexity of studies increase, large samples will be needed to draw reliable conclusions about how early adversity might lead to depression in youth. The practicalities of obtaining such samples, however, can limit the richness of the phenotypes that currently can be investigated more intensively in smaller studies. In attempting to apply the predictive power of large samples to smaller but more deeply phenotyped samples, He et al. [157] proposed the use of meta-matching, which is based on the formulations that many phenotypes are inter-correlated and that correlation structures can be used in smaller samples to translate the predictive models of a phenotype derived from large-scale data to boost prediction of a different, but likely correlated, phenotype.

Finally, it is important to recognize that adolescent depression is heterogeneous with respect to symptoms and their course, and is often comorbid with other conditions [158]. Thus, depression can have different etiologies and pathophysiology. Although we focused in this paper on biological factors that might link early adversity with depression, there are other environmental and experiential variables and biological processes that are almost certainly implicated in the development of depression in adolescence. We hope that our focus in this paper on four specific factors that might link early adversity with adolescent depression will serve as an impetus for researchers to examine other putative mechanisms underlying this association. Advancing our understanding of the relation between ELS and depression will inform the development of more effective approaches to the prevention and treatment of this debilitating disorder.

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ACKNOWLEDGEMENTS

Preparation of this paper was supported by NIH Grants R37MH101495 (IHG) and F32MH135657 (JPU), the Brain and Behavior Research Foundation Young Investigator Grant (JLB), and the Stanford Maternal & Child Health Research Institute Transdisciplinary Initiatives Program (IHG, JLB). Dr. Pine was supported by the National Institute of Mental Health Intramural Research Program (NIMH-IRP) project ZIA-MH002782. This research was supported [in part] by the Intramural Research Program of the National Institutes of Health (NIH). The contributions of the NIH author(s) are considered Works of the United States Government. The findings and conclusions presented in this paper are those of the author(s) and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services.

AUTHOR CONTRIBUTIONS

IHG, JPU, JLB, and DSP all contributed to the conceptualization, organization, and writing of this paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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