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Early caregiving and human biobehavioral development: a comparative physiology approach

Amie A Hane[1,2] and Nathan A Fox[3]

A large and growing body of evidence demonstrates associations between quality of the early caregiving environment and risk for stress-related illness across the lifespan. The recent research examining associations between early caregiving environments and subsequent development is reviewed, with particular attention to early programming and subsequent malleability of systems underlying stress responsivity. A developmental comparative physiology model is suggested; one in which postnatal programming and phenotypic plasticity act in concert as mechanisms underlying the persisting effects of early care environments for biobehavioral outcomes.

Addresses
[1] Department of Psychology, Williams College, 18 Hoxsey Street, Williamstown, MA 01267, United States
[2] Division of Developmental Neuroscience, New York State Psychiatric Institute, New York, NY, United States
[3] Department of Human Development and Quantitative Methodology, University of Maryland, College Park, 3304 Benjamin Building, College Park, MD 20742, United States

Corresponding author: Hane, Amie A (ahane@williams.edu)

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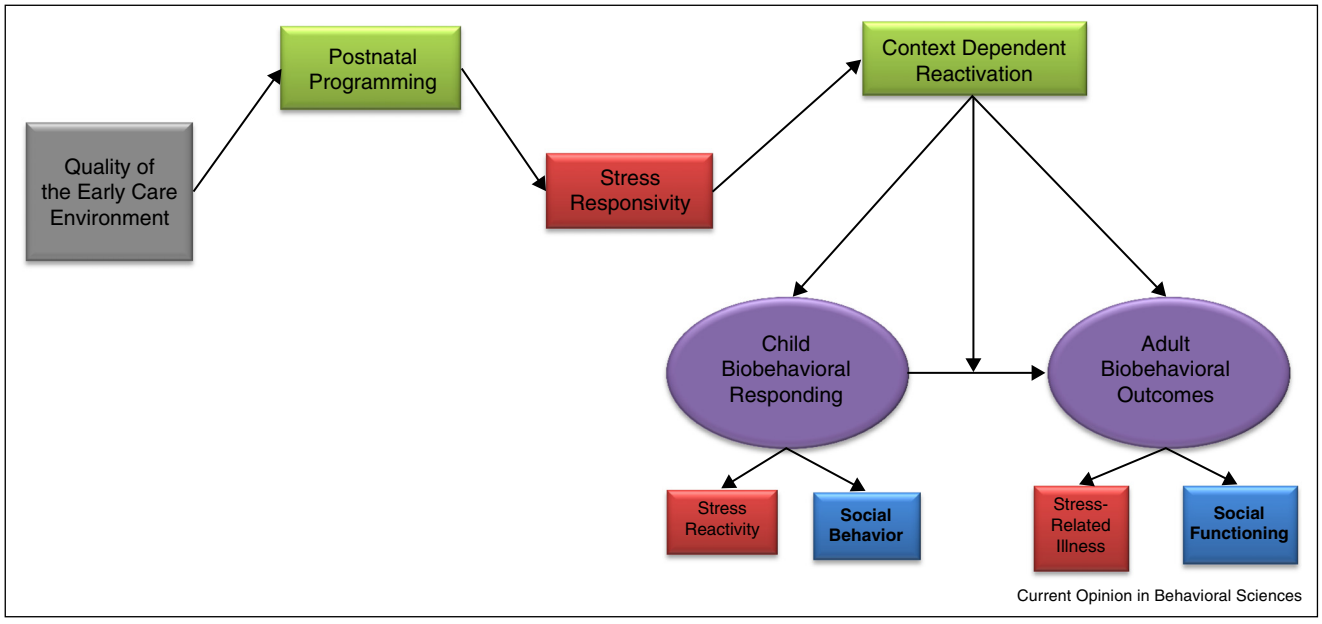
The field of human development has been inundated with evidence documenting the toxicity of early life stress as a risk factor for lifelong physical and psychiatric disorders. Evidence drawn from large epidemiological studies shows that adults reporting higher levels of childhood adversity report poor health outcomes across the lifespan, including sleep disturbance [1]; risk for autoimmune disease [2]; and risk for mental health disturbance [3,4] Adversity in the early rearing ecology appears to set into motion a cascade of stress and physiological responses that undermine long-term health. For instance, the accumulation of adverse events from early-childhood to middle-childhood is associated with elevated biomarkers of inflammation in adolescence [5]. Chronicity of adversity over childhood magnifies the effects of each new stressor, leading to individuals who are less capable of adapting to later life stress given vulnerability imparted by earlier exposures [3]. Elucidating the mechanisms underlying the early programming of stress physiology is imperative to heading off the cascade of exacerbated risk for reduced health and quality of life that begins in the early care environment (ECE) (Figure 1).

There are multiple sources of evidence for the biobehavioral consequences of extremely adverse ECEs on child and adult outcomes. These include exposure to painful procedures in the neonatal intensive care unit [6], childhood maltreatment [7] and the global deprivation of institutionalization [8]. Together this evidence supports the importance of the quality of the ECE for the development of stress physiology. Less extreme gradations in the quality of the ECE also show that low quality maternal caregiving behavior (MCB) is associated with suboptimal biobehavioral outcomes [9–11]. Here we review research demonstrating that the ECE predicts biobehavioral development of the child, with particular attention to postnatal programming and phenotypic plasticity of systems underlying stress responding. We integrate both neuroscience and ecological research as sources of potential mechanisms underlying these effects. A developmental comparative physiology model [12•] is suggested; one in which postnatal programming and phenotypic plasticity act in concert as mechanisms underlying the persisting effects of ECE for biobehavioral outcomes.

Early maternal care and postnatal programming

Maternal caregiving in early infancy sets the stage for biobehavioral adaptations that are to become the basis for stress responsivity and regulation to challenges in the environment. Central to Bowlby's attachment theory is that the infant is prepared to seek proximity to a primary caregiver who serves as a source of safety and comfort in the face of fatigue, distress or threat [13]. Hofer [14•] has provided psychobiological evidence to support this, showing that the acute response to maternal separation seen in infantile rodent offspring results from the loss of the individual components packaged within maternal care (i.e., warmth, satiety, tactile stimulation), each of which plays a critical role in supporting homeostasis in pups.

Figure 1



Quality of early caregiving influences biobehavioral development in humans: a model of phenotypic plasticity. The quality of the early care environment (ECE) gives rise to differences in stress responding through *Postnatal Programming* (including epigenetic alterations) of the systems that regulate physiological stress responding. This programming primes the child by eliciting defensive and adaptive biobehavioral stress responding in the ECE. The child is also primed to respond with the same defensive biobehavioral responding upon exposure to future stressors across development via the process of *Context Dependent Reactivation*. Each subsequent exposure to new stress across development yields increased vulnerability for the child on the basis of malleability to stress responding acquired in the ECE, as programmed defensive responses are reactivated. Reactivation first, occurs when the child is confronted with similar stressors in the future; second, can be considered adaptive in the ECE but maladaptive in less stressful contexts; and third, may be associated with continued dynamic shifts in the epigenome that ultimately give rise to stress-related illness and difficulties in social functioning across the lifespan.

The regulatory capacity of maternal care depends upon the quality of caregiving behavior. Naturally occurring individual differences in the rodent in the frequency of licking and grooming (LG) behavior are associated with alterations in central corticotropin-releasing factor and stress responsive systems [15] and accompanying behavioral differences that persist into adulthood. Rat pups that experience low levels of LG display, as adults, a stress-reactive neuroendocrine profile [16] and a corresponding behavioral profile of elevated stress reactivity [17,18]. These effects are mediated by epigenetic alterations to stress-related genes, with high (relative to low) LG offspring showing decreased DNA methylation of the glucocorticoid receptor region of the hippocampus, which is associated with the reduction in stress responding documented in high LG offspring [19••].

Early care and postnatal programing in humans

Rodent models affirm the developmental relevance of early-occurring maternal care to biobehavioral development via postnatal programming that is accompanied by epigenetic alterations to systems underlying stress responding. Parallel examples exist in the human literature. Similar to the rodent model, ordinary variations in the quality of maternal care in full-term healthy infants is associated with phenotypic changes associated with increased stress and social difficulties [10]. Within the context of a large, longitudinal study of low-risk mothers and their nine-month-old infants, mothers and infants were observed in the home and rated for quality of maternal behavior for sensitive, non-intrusive interventions during the course of routine care in the home (feeding, application of lotion, and dressing). A quality of maternal caregiving behavior (MCB) variable was derived from ratings of maternal sensitivity. Relative to infants who received high quality MCB, those who experienced low quality MCB displayed a stress-reactive biobehavioral profile, marked by more fearfulness during the presentation of novel stimuli, less positive joint attention to a shared object with an unfamiliar experimenter, and more negative affect during mother–child interaction. Infants who experienced low quality MCB also showed a pattern of resting relative right frontal EEG

asymmetry, which previous research has shown to be associated with higher basal and stress-induced salivary cortisol concentrations in 6-month-olds [20] and withdrawal motivation across early development [21]. These findings suggest that 'ordinary' variations in the quality of the early caregiving environment yields contemporaneous phenotypic changes to the systems involved in regulation of stress — effects that closely parallel the rodent postnatal programming models.

Quality of maternal care may have important implications for the neurological substrates that influence subsequent parenting behavior. For instance, relative to mothers who retrospectively perceived high quality maternal care in childhood, those who retrospectively perceived experiencing low quality maternal care in childhood showed more activation of the hippocampus when exposed to infant crying [22]. Such hippocampal activation to infant crying may suggest that early maternal care influences maternal neural response to parenting-related stress in adulthood [23]. This profile of neural activation of stress in the context of parenting may be a function of the reactivation of stress that originated in the ECE. The adverse ECE may prime mothers for stress that is reactivated upon exposure to the context of parenting in the future via the mechanism of phenotypic plasticity.

Phenotypic plasticity

Evolutionary biology has long documented the phenomenon of phenotypic plasticity, defined as the ability of a single genotype to produce different phenotypes on the basis of the demands of the environment [24]. Ecologists offer compelling evidence demonstrating that environmental factors predispose organisms to not only respond defensively, or adapt to their environment; but also to be primed for malleability to mount the same defense again in the future. Reactivation of a defensive adaptation is context-dependent, and occurs when the organism is confronted with the same ecology in the future. An illustration comes from research on the intertidal snails that dwell in rocky tide pools on the coast of Maine. Trussell sampled intertidal snails from two natural habitat conditions — i.e., from tide pools where exposure to predatory green crabs was high; and from tide pools where threat of predation was low. When exposed experimentally to a predatory crab in the laboratory, the snails that were sampled from tide pools with high risk of predation showed morphological changes — exhibiting significantly greater shell density growth and smaller body size than snails sampled from tide pools in which the risk for predation was low [25]. In essence, ecological adversity primed these organisms for change, increasing malleability, thereby insuring that a defensive response would be mounted more readily, or reactivated, when encountering threat in the future. Reactivation is also dose-dependent, as the amount of shell density growth was influenced by the intensity of the risk for predation [26]. The defense is formidable, as the denser shell is also stronger and the reduced body size limits the crab's accessibility to the snail's soft tissue [26]. The stress of predation is associated with a decrease in growth efficiency associated with less foraging behavior, thereby making the snail a less efficient source of energy for its predator [27]. However, each exposure to predatory risk adds the additional burden of carrying the weight of the thicker shell along with the accompanying reduced body mass.

Contemporary research provides evidence for epigenetic mediation of phenotypic adaptations [24]. The intertidal snail shows transcriptional alterations in RNA in response to thermal stress and risk for predation, and the profile of transcriptional activity is distinct for each type of stressor [28]. Recent evidence from another intertidal organism, the sea urchin, highlights the developmental nature of phenotypic plasticity. Sea Urchin larvae float freely in open waters before settling into intertidal habitats. The larvae are commonly confronted with food (i.e., algae) scarcity. Food-deprived larvae adapt with morphological changes, including development of longer arms and reabsorption of stomach tissue, leading to smaller rudiments. These morphological changes are associated with epigenetic differences — when experimentally compared with well-fed larvae, starved larvae show epigenetic alterations to the genes responsible for metabolic rate, growth, mitochondrial activity, regulation of homeostasis, and resistance to stress [29]. Together these examples from the ecology literature highlight two points: First, when faced with adversity organisms adapt to their situation with significant morphological changes. And second, the mechanisms for these adaptations appear to be epigenetic in nature. Both of these processes may be present in the human response to adversity as well.

Early care environments and phenotypic plasticity

In the rodent model, it has been suggested that a general profile of *defensive reactivity* develops in low LG rodents because behavioral defensiveness and the associated release of stress-related hormones are adaptive, allowing for detection of threat and the mobilization of metabolic resources under suboptimal early care conditions [30]. Much like the intertidal snail, this mounting of a defensive response may serve to prime the system to mount such a reaction in the future under similar environmental conditions, and to do so more readily than others of the same species reared under less aversive conditions.

Phenotypic plasticity is also applicable to humans, with infants showing both a behavioral and physiological defensive response during the experience of low-quality

caregiving. Hane and Philbrook observed mothers as they undressed, bathed, and re-dressed their 4–8 week old full-term infants in the home and MCB was coded. Salivary cortisol was measured in infants before tub bathing and again 15 minutes following removal of the neonate from the bath water. Infants of mothers who provided lower quality MCB showed a significantly larger increase in cortisol (over basal levels) following this experience of routine care [9]. Hence, the experience of being cared for by an insensitive caregiver early in life was associated with elevated stress responding linked to the early care experience.

A growing body of literature demonstrates that ECEs are associated with epigenetic alterations in peripheral tissue sampling in humans [31–35] and this research is consistent with the phenotypic plasticity model.[1] Table 1 highlights four studies that document that epigenetic changes are dynamically linked to the ECE, with evidence of change over time as a function of prolonged exposure to adversity. For example, in preterm infants, the experience of the NICU itself is associated with epigenetic changes in methylation over time, varying from birth to postnatal day four [32] to time of discharge from the NICU [31]. In institutionalized children, epigenetic alterations to telomere length is associated with duration of time spent in the institution [33], with a steady decrease in telomere length from ages 8–14 for children who remain institutionalized [36]. Hence, epigenetic markers are further altered as exposure to adversity increases. It may not be surprising then that widespread changes in methylation across the genome have been found for children with a history of earlier exposure to maltreatment [35] and in adolescents with exposure to high levels of parental stress [34]. Dramatic epigenetic changes associated with a history of adverse ECEs by middle childhood and adolescence may be the result of continual epigenetic changes that accumulate across time as exposure to adversity or new stressors are encountered.

Context-dependent reactivation

There is also support for context-dependent reactivation of stress responding on the basis of features of the ECE. Even a singular disruption to mother–infant interaction may lead to context-dependent reactivation. Six-month infants were brought to the lab and randomly assigned to either a mother–infant face-to-face interaction (control group) or the maternal still-face paradigm (SFP). The infants who were confronted with the maternal termination of contingent responsiveness in the SFP showed a significant increase in salivary cortisol following the SFP. When brought back to the laboratory the next day, placement of the infant in the same context, but not proceeding with the SFP resulted in reactivation of the cortisol response for infants in the SFP condition. No such effect was found for control infants on days 1 or 2 of the experiment.

Additional evidence comes from the rodent and human maternal care literatures. If the receipt of insensitive care in the early relational context primes the system for defensive responding in similar contexts, then social interactions with others may trigger reactivation of stress physiology. One might expect that offspring who experience stress during early care may have difficulties later on while interacting with peers. This too is supported by animal models. Juvenile male offspring who received low LG as pups engaged in more play fighting in multiple play partners housing than high LG males [37] and adult offspring receiving low LG as pups manifested more aggressive and defensive behavior during a resident-intruder test, as compared to adult offspring who received high LG as pups [38]. The ECE of the human is also associated with a profile of defensive play behavior with peers. In a longitudinal follow-up of MCB and biobehavioral responding, we found relative to children who experienced high quality MCB as infants (high MCB children), those who received low quality MCB (low MCB children) continued to show increased stress reactivity on measures that parallel those used in our earlier report, including inhibited social behavior with adults and right frontal EEG asymmetry [11]. As well, low MCB children manifested more aggression during play with a novel peer than low MCB children. Mothers reported that low MCB children tended to show more internalizing problems and more proneness to anger in social situations.

Additional support for defensive reactivation as a function of ECE is present for children exposed to more extreme adversity in the ECE. Longitudinal follow-up of a children born very preterm shows that higher exposure to procedural pain (routine blood draw) is associated with reduced cortisol responding to acute pain at age four-months [39] and lower basal cortisol and less variable diurnal rhythms in cortisol at school age [6]. Children who were institutionalized in infancy also exhibit differences in stress responding later in childhood [40]. In a longitudinal follow-up of children from the Bucharest Early Intervention Project [41•], children underwent the Trier Social Stress Test (TSST) at age 12 and neuroendocrine and autonomic stress responding were examined. Relative to children who were randomly assigned to foster care, continually institutionalized children showed blunted cortisol responding across the stress task. Autonomic responding was also blunted for the continually institutionalized group, in terms of heart rate, diastolic blood pressure, and pre-ejection period. Placement into foster care before ages 18–24 months was significantly associated with the increase in stress physiology, similar to

[1] An extensive review of epigenetics and ECEs for humans is beyond the scope of this review, readers are referred to Boyce and Kober [57••]

Table 1

Summary of research demonstrating change over time in epigenetic alterations linked to early care environments.

Early care environment	Citation	Nature of study sample	Type of peripheral tissue and age at DNA sampling	Epigenetic alteration	Functional significance
Neonatal Intensive Care Unit	Provenzi *et al.* [31]	56 children born very preterm (24–28 weeks gestation) and 32 full-term controls. Very preterm infants were divided into high ($n = 31$) versus low ($n = 25$) exposure to procedural pain (skin-breaking procedures) while in the NICU	Cord blood (at birth) and peripheral blood (in the very preterm group only at time of hospital discharge)	Methylation at 20 CpG sites within the promoter region of the *SLC6A4* gene was examined. No differences were found at birth between very preterm and full term infants. Relative to very preterm infants who experienced lower procedural pain, those who experienced high procedural pain were found to have significantly increased methylation at CpG sites 5 and 6 at time of discharge.	Higher *SLC64A* methylation is associated with intrasynaptic serotonin signaling, yielding increased serotonin concentrations consistent with biochemistry of depressed and anxious adults.
	Kantake *et al.* [32]	40 infants (20 full term and 20 preterm)	Cord blood at birth and peripheral blood at postnatal day 4	Methylation rates in the 1-F promoter region of the glucocorticoid receptor gene in 33 CpG sites were examined at birth and postnatal day 4. In preterm infants, methylation rates significantly increased at multiple sites from birth to postnatal day 4. Methylation rates remained stable in full-term infants.	Increased methylation of the glucocorticoid receptor gene is associated with a decrease in the sensitivity of immune cells to glucocorticoid hormones that are involved in terminating inflammatory processes and may be a mechanism underlying increased risk for adrenal insufficiency.
Institutionalization	Drury *et al.* [33]	Longitudinal follow-up of 64 children enrolled in the Bucharest Early Intervention Project [41•] including 28 children who remained in the institution and 36 children who were placed in foster care.	Buccal cells acquired once in children ranging in age for 6–10 years	Percent of time spent in institutional care was significantly associated with shorter telomere length. This association remained significant when controlling for study group (foster care or institutionalized), gender, ethnicity, low birth weight, and age at DNA sampling.	Decreased Telomere length is a marker for biological aging and is associated with cardiovascular disease, diabetes, obesity, and health risks related to early adversity.
	Humphreys *et al.* (submitted for publication)[a]	Longitudinal follow-up of 79 children enrolled in the Bucharest Early Intervention Project [41•] comparing 50 children with a history of institutionalization to 29 never institutionalized children.	Buccal cells acquired repeatedly, (2–4 times) from ages 8–14 years.	Telomere shortening was significantly accelerated over time in children with a history of institutionalization relative to never institutionalized children.	

[a] Humphreys KL, Esteves K, Zeanah CH, Fox NA, Nelson CA, Drury SS. Accelerated telomere shortening: tracking the lasting impact of early institutional care at the cellular level (submitted for publication).

that found in the never institutionalized community controls. Hence, there may be a sensitive period for ECE programming of stress physiology [40]. Autonomic responding is also dampened upon reactivation in children with a history of abuse/neglect. Children with a history of maltreatment failed to show an increase in blood pressure in response to a social laboratory stressor; while non-maltreated children showed a significant increase to the laboratory stress paradigm [7]. Hence, for instances of extremely adverse ECE's, defensive reactivation manifests as a less variable, or blunted physiological response to stress, indicative of physiological dysregulation that is specific to the nature of the ECE.

When does reactivation become maladaptive?

Adverse rearing ecologies prime the system to adapt to the conditions within which development ensued. The infant of a low MCB mother benefits from the activation of stress physiology to meet the metabolic demand of discomfort. When remaining in the context of ecological adversity, increased reactivity and defensive adaptations may be advantageous for survival. For instance, in the rodent, female offspring of low-LG and mid-LG dams show play dominance and are particularly likely to engage in pinning behavior when female peers are in estrus, which may promote their social rank and reproductive advantage in competitive environments in which resources are scarce [42]. Female children of mothers who were rated as high in maternal harshness in early childhood were significantly more likely to reach menarche earlier, and early menarche was predictive of sexual risk-taking behavior [43]. Hence, programming from the early rearing environment may result in activation of defensive responding that is adaptive for offspring who remain in harsh ecologies. Ellis has suggested that 'fast' life history strategies promote reproductive success at an earlier age for offspring whose ecology forecasts less longevity [44••].

The low MCB child epigenetically programmed for heightened stress responding may manifest context-dependent reactivation of stress responding in each new social setting outside of the home. When the formative social experience offered by mother signals discomfort and stress in the presence of another, each new social context thereafter may grow increasingly more difficult to navigate, as the increase in stress physiology and defensive reactivation costs the individual, becoming a thicker shell and a heavier burden over time. The physiological load of continually heightened stress in the social world is carried within the child, creating anxiety in early childhood [11,45] that may influence cardiovascular health beginning in childhood [46] and inflammatory responses that compromise immune health into adulthood [47].

More troubling is that the system is primed for reactivation under extremely adverse ECE. Institutionalized infants adapt to multiple caregivers with indiscriminate sociability. This is adaptive in the institution, where indiscriminate sociability ensures receipt of care — the child who reaches out to more caregivers is more likely to receive care. However, under conditions of lower adversity, this behavior is maladaptive, diagnosed as Reactive Attachment Disorder, and interferes with the development of a healthy attachment to a singular primary caregiver [48]. Maltreated children show greater ERP responding to angry (versus sad or neutral) faces, which is adaptive when the child's sensitivity to the affective valence of the abusive caregiver signals impending danger. However, in the non-abusive context outside of the home of origin, this type of hypervigilance to mood interferes with attentional resources that need to be directed toward learning and healthy social functioning [49]. The long-term health consequences of altered stress physiology as seen in low MCB children, NICU survivors, institutionalized infants, and maltreated children may result in lifelong risk for developmental psychopathology, as context-dependent reactivation continues to occur across the lifespan.

Context dependent reactivation in adulthood

Phenotypic plasticity as a function of the ECE and the associated epigenetic alterations are not limited to childhood. There is evidence for reactivation of defensive responding from stress encountered in adulthood in rodent models. For instance, female adult offspring who experienced repeated postnatal maternal separation in the first two weeks of life (in comparison to non-handled controls), were assessed for anhedonic responding after exposure to stress introduced in adulthood. Postnatally maternally separated rats showed a blunted anhedonic response to an initial acute exposure to social defeat (pinning by a male resident-intruder), but an elevated anhedonic response was found after 7 daily exposures of the same social defeat paradigm. Hence, the ECE predicted later reactivation characterized by an initial protection against the anhedonic response to a single social stressor, but a swift reactivation, with an increased anhedonic response, when confronted with the same social stressor repeatedly [50•]. Further, joint exposure of postnatal maternal separation (versus handling or normal rearing) and adulthood stress (novel cage or social defeat) was associated with increased *slc6a4* mRNA expression in serotonergic neurons only for rats that experienced postnatal separation *and* social defeat in adulthood. Hence, subsequent social stress in adulthood further increased the epigenetic alterations associated with dysregulation of the serotoninergic systems involved in depression and anxiety resulting from the ECE [51]. In the human, early life trauma, and particularly child abuse, is associated with PTSD in adulthood following exposure to re-victimization in adulthood, particularly when both the ECE and the later life trauma are contextually similar [52]. Depression is associated with inflammatory processes that are associated with early-life exposure to stress [53]. In a study of depressed men with and without a history of

early life trauma, only depressed men with a history of early adversity showed an increase in inflammatory response (increased proinflammatory markers in plasma and DNA binding) to the TSST [54••]. Depressed women with a history of depression and a history of child abuse showed significantly higher neuroendocrine responding to the TSST (greater plasma ACTH and cortisol concentrations) relative to depressed women with no abuse history and community controls [55]. Taken together, this evidence suggests that stressful life events in adulthood may reactivate programmed stress responding that originated in the ECE, particularly when the context of reactivation shares features of the ECE, i.e., social stressors in particular. Reactivation of stress physiology throughout the lifespan may also give rise to further increases in epigenetic alterations that originated in the ECE.

Summary and conclusions

Animal models and studies in humans indicate that adverse early care environments program the system via epigenetic alterations to the systems responsible for biobehavioral stress responding [31,32,56]. Here we suggest that developing stress physiology is phenotypically plastic. Recent advances in the field of ecology show that phenotypic plasticity is mediated by epigenetic changes induced by the ecology of early development [29]. Context-dependent reactivation of postnatal programming as a function of the ECE may be the mechanism underlying the significant health footprint left in the wake of suboptimal care [1–4]. As infants reared in adverse ECE's enter new social contexts, the burden of early adversity carries with them; setting into motion the cascade of context-dependent reactivation of defenses initially acquired in the ECE. These adaptations triggered by formative social experiences carry over to new social contexts, when they may no longer be of adaptive value, increasing the likelihood of reactivation in each new stressful context, which further contributes to more stress-related vulnerability. Context-dependent reactivation and the accompanying epigenetic changes remain ongoing processes across development that accumulates risk for the plethora of stress-related illnesses across the lifespan of individuals who experienced early adversity [1–4] — be it nuanced differences in the quality of maternal care or extreme instances of adversity.

Conflict of interest

Nothing declared.

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Glossary

Early Care Environment (ECE): Refers to the characteristics of the rearing environment. Across species, this includes the elements of the caregiving environment that reduce or activate stress responding in offspring. In the human these include insensitive maternal caregiving behavior and exposures to extremely aversive conditions, such as parental separation and procedural pain of the Neonatal Intensive Care Unit; parental separation and global neglect of institutionalization; and parental maltreatment of the child, which includes neglect and abuse.

Postnatal Programming: Drawn from rodent models of maternal care, refers to the processes through which quality of maternal caregiving behavior, defined in terms of high or low frequencies of licking/grooming behavior (usually occurring in the context of arch-backed nursing), in the first two weeks of life, induce changes in the behavioral and physiological regulation of stress that result in altered behavioral and physiological differences that persist across the lifespan. These effects are mediated by epigenetic changes, alterations in the expression of genes involved in regulation of stress and stress-related illness [19••].

Phenotypic Plasticity: Drawn from ecology and research in lower life forms, refers to the ability of a single genotype to produce more than one phenotype on the basis of the demands of their environment [24]. The differential expression of a phenotype depends upon these environmental demands, which elicit adaptive/defensive responses in organisms in response to adversity (e.g., food scarcity, climate change, and risk of predation) that result in morphological changes. On the basis of exposure to the challenges of the environment of origin, the organism then becomes phenotypically flexible, and will mount the same defense again in the future. These effects are also associated with transcriptional alterations in the candidate genes associated with the biochemical processes underlying the altered phenotype [24,28].

Context Dependent Reactivation: A term extrapolated from the phenotypic plasticity literature, here we refer to the human response in which infants, children, or adults previously programmed for behavioral and physiological stress by the elements of an adverse ECE show reactivation of the stress response when encountering future stressors — particularly stressors that share contextual features with the stress-inducing features of the ECE (usually social stressors, as the context of early care represents the formative social experience).

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