



Epigenetic Markers of Early Life Stress and Emotional Regulation in the Development of Stress-Related Psychopathology

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ABSTRACT

Early life stress (ELS) is a potent environmental factor that shapes vulnerability to stress-related psychopathology across the lifespan. Converging evidence indicates that adverse experiences during sensitive developmental periods alter neurodevelopmental trajectories through epigenetic mechanisms that regulate stress-responsive gene expression. This review synthesizes findings on how ELS induces persistent epigenetic modifications—such as DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA regulation—in key biological systems involved in emotional regulation, including the hypothalamic–pituitary–adrenal (HPA) axis and limbic circuitry. Genes central to stress responsivity and neural plasticity, including NR3C1 and BDNF, emerge as critical epigenetic targets linking early adversity to dysregulated emotional processing and heightened risk for anxiety, depression, and related disorders. Emotional regulation is highlighted as a central mediator through which epigenetic programming translates early environmental exposure into long-term behavioral and psychiatric outcomes. Understanding these epigenetic signatures provides insight into mechanisms of developmental vulnerability and resilience and offers promise for identifying biomarkers and intervention targets for stress-related psychopathology.

Keywords: *early life stress, epigenetics, emotional regulation, DNA methylation, histone modifications, non-coding RNA, HPA axis, stress-related psychopathology, neurodevelopment, anxiety, depression.*

INTRODUCTION

Psychological disorders emerge from interactions between genetic, social, and environmental determinants (C. Jawahar et al., 2015). Psychological disorders emerge from interactions between genetic, social, and environmental determinants. Stressful or threatening experiences during early life can disrupt the

developmental timing of the brain, affecting the growth and organization of neural circuits, thereby leading to emotional dysregulation and increased risk of psychiatric disorders, such as anxiety, depression, and post-traumatic stress disorder (PTSD). Epigenetic mechanisms that modify the expression of genes involved in stress response represent a biological process through which early life stress (ELS) regulates the emotional development of the brain. Stressful, terrifying, and threatening experiences during early life dramatically alter the sequencing of multiple events, disrupting the developmental timing of the brain and disturbing the growth and organization of various neural circuits. Accordingly, personality and temperament can be deeply disrupted, leading to emotional dysregulation and increased risks for developing various psychiatric disorders. Early life stress (ELS) represents one of the most powerful examples of psycho-environmental influences on the developmental programming of stress-related psychiatric conditions.

Theoretical Framework

The literature consistently documents the crucial role of the early environment during critical development windows in predisposing individuals to the development of different types of psychopathology, including behaviour disorders, mood disorders, and substance use disorders (Murgatroyd & Spengler, 2011). Associated with these adverse circumstances are detectable epigenetic changes in post mortem tissue and, in some cases, biofluids. Such epigenetic modifications may persist through a lifetime and govern stress-related neurobiological, emotional, and behavioural outcomes after exposure to early life adversity (C. Jawahar et al., 2015).

Early Life Stress and Developmental Psychopathology

Sexually dimorphic vulnerabilities to depression arise from differences in hormonal, genetic, and behavioral factors that interact developmentally with adverse experiences. Environmental influences, notably the nature of early-life adversity, are critical to shaping the risk of psychopathology. Early stress fosters emotion dysregulation, and a strong body of evidence associates dysregulated emotion with later depressive symptoms. How does the early stress–emotion dysregulation connection emerge? One possibility is that stress induces epigenetic alterations governing emotion-regulation circuitry, including HPA-axis and mesolimbic dopamine systems. A distinct model integrates early stress, epigenetic reprogramming, and emotion-regulation disturbance to account for sexually dimorphic risk—the only such model within the epigenetic literature. This framework specifies epigenetic targets, including BDNF and Nr3c1, and maps the neurobiological circuits of effect, signalling distinct phases in the ontogeny of the early stress–stress-vulnerability cascade (Murgatroyd & Spengler, 2011). Early life stress (ELS) increases vulnerability to affective disorders, schizophrenia, and aggressive behavior, and ELS-type stress is linked to disorders including depression, anxiety, and poor impulse control. The HPA axis and serotonergic systems underpin the development of these disorders, and enduring stress-induced alterations impair their regulatory functions. ELS–epigenetics models make several precise stipulations about hormones and HPA signalling. The continued exploration of ELS–epigenetics hypotheses in the sexist framework may clarify the neurodevelopmental events that specify the sex bias in stress-related psychopathology and advance understanding of the neurobiology and treatment of stress-dependent disorders (C. Jawahar et al., 2015).

Epigenetic Mechanisms in Stress Response

Early life stress (ELS) elevates the risk for the development of psychiatric disorders such as major depressive disorder, anxiety disorders, addiction, and schizophrenia during childhood and across the life span. ELS impacts development of the hypothalamic-pituitary-adrenal (HPA) axis and patterns of stress hormone secretion, thereby influencing emotional behavior, learning, and memory. ELS alters development of brain circuits involved in emotional regulation and modifies the neuroplastic framework during critical and sensitive periods of early brain development, which may reshape the ability to modulate negative emotions. Exposure to a wide variety of ELS, such as childhood abuse, neglect, poverty, and parental illness, is prevalent and affects 10 to 30% of children worldwide. ELS can reinforce maladaptive behavior, making it difficult to adjust to social environments, and is co-morbid with a high frequency of other chronic health

conditions. At the molecular level, ELS alters the epigenetic signature of the stress-regulating gene NR3C1 (encoding the glucocorticoid receptor) and modifies the transcriptional activity of its promoter region. Epigenetic alterations may exhibit transmission across multiple generations, providing a biological basis for the transmission of the psycho-emotional burden originating from ELS (C. Jawahar et al., 2015). Chronic stress down-regulates the expression of DNA methyltransferases (DNMTs) and induces the opposite expression pattern of ten-eleven translocation (TET) enzymes, leading to a significant loss of DNA methylation in genes associated with stress responsivity. In addition to DNA methylation, ELS affects histone acetylation and transcription levels between the prefrontal cortex and the hippocampus, and these epigenetic alterations at both the DNA and histone levels are detectable in peripheral blood, providing the possibility of developing blood-based biomarkers for ELS exposure (Matosin et al., 2017) [table 1].

Table 1: Early Life Stress, Epigenetic Mechanisms, and Emotional Regulation

Component	Description	Biological Targets	Functional Consequences
Early Life Stress (ELS)	Exposure to abuse, neglect, poverty, parental illness, or chronic adversity during sensitive developmental periods	Developing brain, endocrine system, stress-regulation circuits	Disrupts neurodevelopmental timing and increases vulnerability to psychopathology
Stress-Response Systems	Systems regulating stress and emotion during development	HPA axis, serotonergic and mesolimbic dopamine pathways	Alters cortisol regulation, emotional reactivity, and stress sensitivity
Epigenetic Programming	Environmentally induced regulation of gene expression without DNA sequence changes	DNA methylation, histone modifications, chromatin accessibility, non-coding RNAs	Produces long-lasting changes in gene expression profiles
Key Stress-Related Genes	Genes involved in stress regulation and neuroplasticity	NR3C1 (glucocorticoid receptor), BDNF	Modulates stress responsivity, emotional regulation, and neural plasticity
Emotional Regulation	Ability to modulate emotional responses to stress	Prefrontal cortex–amygdala–hippocampus circuitry	Dysregulation mediates the link between ELS and later psychopathology
Psychopathological Outcomes	Stress-related mental disorders emerging across the lifespan	Anxiety disorders, depression, PTSD, schizophrenia, addiction	Increased risk due to persistent epigenetic and neurobiological alterations

Emotional Regulation as a Mediator

The hypothesis linking dysregulation of emotional regulation to the aetiology of stress-related psychopathology is well-supported in the literature (C. Jawahar et al., 2015). A growing body of research indicates that the impact of early life on the development of emotional regulation cannot be underestimated.

Numerous studies have demonstrated that deficits in emotional regulation are associated with the emergence of mental health problems across the lifespan. Stressors during prenatal development, early life, or childhood have been linked to changes in brain and behaviour; such factors are considered early-life stress (ELS). Early-life environmental events have been shown to mediate the effect of ELS on the manifestation of psychopathology.

Epigenetic Signatures of Early Life Stress

The hypothesis that epigenetic modifications are associated with early life stress (ELS) and that those modifications influence developmental trajectories connected to stress-related psychopathologies is supported by substantial evidence. The molecular consequences of ELS include not only a mere change in the number of active genes, but also tissue- and cell-specific departures from the factory-like operation of the genome. Epigenetic mechanisms such as DNA methylation, post-translational histone modifications, changes in chromatin accessibility, and non-coding RNAs play a major role in orchestrating these massive restructurings of gene expression patterns and in conveying the consequences of ELS on physiological and behavioural circuits connected to stress and emotional control (C. Jawahar et al., 2015). These early epigenetic programming events have been shown to remain detectable throughout life and to constitute a formative window for the establishment of elaborate sequences of gene activity that configure the responses to stress during postnatal development and ageing. Stress-inducing events during sensitive periods of brain maturation such as birth, weaning, or puberty can subsequently affect behaviour and increase susceptibility to mental disorders. Stress-responsive genes remain unstable and exhibit modified sensitivity or plasticity long after ELS exposure has ceased, influencing the fate of stress-induced behaviours and managing the transition to adult patterns of activity in neurodevelopmental conditions. Stressful experiences occurring early in life, therefore, can induce widespread and persistent epigenetic changes at the cellular level that ultimately shape the entire organism [table 2].

Table 2: Epigenetic Signatures of Early Life Stress and Their Role in Psychopathology

Epigenetic Mechanism	Molecular Characteristics	Evidence from ELS Studies	Impact on Stress-Related Disorders
DNA Methylation	Addition of methyl groups to CpG sites leading to gene silencing	Increased NR3C1 methylation in individuals exposed to early adversity	Impaired glucocorticoid receptor expression and dysregulated HPA-axis activity
Histone Acetylation	Acetylation associated with open chromatin and gene activation	Altered HAT and HDAC activity following ELS	Disrupted transcription of genes involved in emotional regulation
Histone Methylation	H3K4me3 linked to active genes; H3K9me3 and H3K27me3 linked to repression	ELS induces region-specific histone methylation changes	Long-term repression or sensitization of stress-responsive genes
Chromatin Accessibility	Structural remodeling enabling enhancer–promoter interactions	ELS modifies chromatin openness in prefrontal cortex and hippocampus	Alters transcriptional responsiveness to future stress
Non-Coding RNAs (ncRNAs)	Regulatory RNAs controlling gene networks	ELS-induced changes in miR-30a expression	Dysregulation of neurodevelopmental and emotional pathways

Transgenerational Effects	Epigenetic marks transmitted across generations	Persistent DNA methylation patterns observed in offspring	Intergenerational transmission of stress vulnerability
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DNA Methylation Patterns

In the nervous system, DNA methylation is a silencing mechanism that modulates gene expression through the addition of a methyl group to cytosines in the context of cytosine-guanine (CpG) dinucleotides. Past studies have linked increased DNA methylation of the snakehead glucocorticoid receptor gene (*Nr3c1*) to early-life stress (ELS) in rodents, which similarly affects the early-life environment in humans. These early patterns of methylation continue into adulthood, and peripheral blood DNA from a cohort exposed to highly stressful perinatal events exhibited marked increases in *NR3C1* methylation (J van der Knaap et al., 2014). In a mouse model, heightened maternal licking and grooming increased global levels of certain DNA methylation marks, while different ELS experiences produced distinct profiles of DNA methylation change in specific neural populations differentially linked to the developing rodent and human HPA axis (Catale et al., 2020).

Histone Modifications and Chromatin Accessibility

Significant pre- and post-natal environmental and epigenetic events affect gene transcription and the histones associated with DNA. These post-translational modifications alter the formation of chromatin, modulating gene activity. Acetylation is the dominant modification associated with gene activation, while tri-methylation of H3K4 is also linked to active genes and poised genes that can be rapidly turned on (C. Jawahar et al., 2015). On the other hand, tri-methylation of H3K9 and H3K27 and, to a lesser extent, H4K20 are associated with transcriptionally silent chromatin. Proteins such as Histone deacetylases (HDACs) and Histone Acetyltransferases (HATs) mediate chromatin changes by adding or removing acetyl groups to NAC. The protein methylation process is mediated by methyltransferase (HMT) activity, while amine oxidases (HDMs) are responsible for demethylation. Chromatin opening promotes not only gene activation but also allows enhancer–promoter interactions that are essential for gene induction. Enhancers are distal regulatory cis-elements that contain DNA-sequence motifs recognized by trans-acting factors. Enhancers can be identified in the genome by assessing chromatin accessibility.

Non-Coding RNAs in Stress Regulation

Early life stress (ELS) is a major risk factor for the development of several stress-related disorders leading to high morbidity in adulthood, including anxiety and mood disorders (Cattaneo et al., 2020). In animal models, ELS alters the expression of microRNA-30a, a non-coding RNA that regulates a wide network of genes involved in neurodevelopment, metabolism, and cell survival, contributing to a phenotype reminiscent of depression. miR-30a was reported to be targeted for DNA methylation by ELS, and the evolution of wide-ranging ELS-affected networks is consistent with the pathogenesis of stress-related disorders. Epigenetic mechanisms taken into consideration for the interplay between ELS and the evolution of stress-related disorders include DNA methylation, histone modifications, chromatin remodeling, and ncRNAs. Both animal and human studies demonstrate that the stress-related gene *Bdnf* and its regulator *ER α* are repressed under anabolic conditions. Down-regulation of these epigenetic regulators or their target genes upon ELS exposure promotes the evolution of stress-related disorders. Chromatin remodeling at the *Bdnf* locus also facilitates the expression of neuronal activity-inducible genes, such as *Egr1*, upon ELS. The HPA axis highly modulates the amount of stress in an early age during which brain circuitries are still developing. The effects of ELS on the stress-system establishment vary accordingly and can trigger anxiety and mood disorders later on.

Neurobiological Pathways Linking Epigenetics and Emotion Regulation

Allostasis is defined as the process of achieving stability through change and is based on the concept of allostatic load, which involves physiological adjustments that optimize performance (C. Jawahar et al.,

2015). In humans, sustained early life stress (ELS) has been linked to psychopathology risk factors such as elevated diurnal cortisol release, altered catecholamine release, and immune functioning dysregulation. These risk factors are associated with the development of stress-related psychiatric disorders. Key physiological systems (the HPA axis, the autonomic nervous system, and the immune system) develop during sensitive periods of childhood and undergo extensive maturation throughout development. Individual experiences translate affect and arousal into neural signal propagation, and these signals interact with gene networks to adjust processes involving phenotypic potential and plasticity in response to stress exposure.

Programming of stress-related and affective psychopathology is also sensitive to timing, dose, and type of ELS, with certain mid-to-late childhood stressors exerting particularly strong impacts. Intensive chronic stress earlier in childhood, such as abuse, has less influence than moderate episodic stress. Programming is also influenced by the environment when stress occurs, and processes that couple timing and type to experience-specific programming of risk are needed to elucidate interdependencies between ELS, affect, gene networks, and phenotypic determinants. Specific ELS types (e.g., parental separation, maternal neglect, abuse, traumatic loss) target different experience-affect-gene axis connectivities, and the programming impacts of parental death and chronic separation during the perinatal period are significantly greater than typical abuse ratios that characterize other developmental periods.

Neuroplasticity permits experience-dependent modulation of stress-related and affective circuits and prospectively links ELS timing and programming characteristics to permanent neural architecture alterations. Locus-specific DNA methylation associated with stress regulation and HPA-axis feedback is maintained in neural stem cells and broadly affects circuits involved in ELS programming. Two primary ELS-affect-architecture-gene programming connections have been identified (Murgatroyd & Spengler, 2011).

Hypothalamic-Pituitary-Adrenal Axis

Stressful experiences during early life influence future vulnerability to psychiatric disorders. The hypothalamic–pituitary–adrenal (HPA) axis mediates the stress response and undergoes significant reorganization throughout development. Early adversity can shape the maturation of HPA systems and stress-responsive circuits in emotional centres, leading to persistent changes in stress reactivity, reduced volume and dysfunction of stress-regulating regions, and an altered neuroendocrine stress response. Stress-induced epigenetic changes may directly regulate HPA axis developmental programmes. Following stress exposure, DNA methylation and histone modifications can alter the expression of transcription factors that govern HPA development and regulate the expression of neuropeptides within stress-sensitive circuits (C. Jawahar et al., 2015) ; (Murphy et al., 2022).

Limbic System and Prefrontal Cortex Circuits

Early life stress modulates the development of interconnected brain structures, including the hippocampus, anterior cingulate cortex, and prefrontal cortex, aspects that can be investigated indirectly through examination of the limbic system and prefrontal circuit, which underpins both mood and anxiety disorders. Moreover, early life stress leads to the disruption of limbic and prefrontal connectivity, and multiple markers of this disruption correlate with stress-related psychopathology (C. Jawahar et al., 2015). The limbic system forms a central hub linking the brainstem to the prefrontal cortex, but this hub also has extensive projections elsewhere and indeed can be considered a fundamental initializing module for the entire brain, implicating it in other functions beyond stress response or regulatory dysfunction. The region contains the amygdala, hippocampus, anterior cingulate, and septal nucleus, and-in terms of eye movement and modulated by emotional state-exclusive projections from the thalamus and sensory structures are related to the choice of target fixation or stimulus searching (Murgatroyd & Spengler, 2011). Moreover, the limbic system plays a central role in the interplay between cognition, emotion, and action, while the prefrontal cortex-defining

features include a highly developed anterior cingulate area with diverse connections to both cognition and limbic structures-relates stimulus and action to anticipated reward or aversion or to interoceptive changes.

Neuroplasticity and Neurotrophic Factors

The effects of early-life stress on the programming of stress-related psychopathologies are mediated through disruption of neuroplasticity (Murgatroyd & Spengler, 2011). Stress during early development alters the epigenetic programming of genes involved in neuroplasticity, including brain-derived neurotrophic factor (BDNF). In stress-sensitive rodent models, early-life adversity selectively induces the hypermethylation of the *Bdnf* promoter in the prefrontal cortex, with diminished exon-specific *Bdnf* expression being observed in adulthood. Adverse maternal care is also correlated with epigenetic modifications of female reproductive and GABAergic signaling pathways, whereas enhanced maternal nurturing is associated with *Bdnf*-expression-promoting epigenetic marks. In contrast, chronic psychosocial stress in adulthood increases *Bdnf*-promoter methylation and reduces *Bdnf* expression in the hippocampus, illustrating the susceptibility of neuroplasticity genes to epigenetic disruption by stress throughout life.

The glial-cell-line-derived neurotrophic factor (GDNF)-signaling pathway is epigenetically silenced following adult psychosocial stress in stress-sensitive rodent strains. Pervasive reductions of *Gdnf* expression in the nucleus accumbens are accompanied by increased promoter methylation and disabling histone-modification patterns, indicating the establishment of a stress-induced *Gdnf* repression program. Transgenic mice with nucleus-accumbens-selective overexpression of GDNF are protected from developing stress-induced behavioral alterations, and pharmacologically activating the GDNF cascade ameliorates the effects of chronic early-life adversities on emotionality.

Programming of Stress-Related Psychopathology Across Development

Scientific evidence shows that early stress alters the developing brain architecture and stress-response systems, predisposing individuals to stress-related psychopathologies later in life. Consequently, early-life interventions hold significant promise for modulating risk (Joachim Raabe & Spengler, 2013). Conversely, chronic anxiety or depressive episodes significantly increase vulnerability and maladaptive programming by reinstating the plasticity of adaptive systems, with the intermittent onset of mild to severe stress or trauma aggravating symptoms (Murgatroyd & Spengler, 2011).

Multiple features illustrate the notion of developmental programming and serve as the basis for future exploration of moderating and additional mechanisms involved in early stress-related changes. Of notable importance, external, internal, and regulatory signals interact to determine the timing, dose, and type of stress and/or perturbed experience that elicit epigenetic changes. The specific stress received and/or condition experienced early, particularly in a critical or sensitive period, may transdefine the subsequent trajectory of neurobiological vulnerability. Additionally, sex differences in programming and a wide range of early-life variables offer a richer understanding of the early period when epigenetic programming and greater susceptibility for later stress vulnerabilities arise.

Critical and Sensitive Periods

Early life stress (ELS) has pervasive long-term effects on emotional health, including increased susceptibility to stress-related disorders, and considerable epigenetic reprogramming has been associated with the transmission of these effects (C. Jawahar et al., 2015). The epigenetic framework provides a compelling paradigm to characterize the influence of early adversity on mental health across the lifespan through distinct epigenetic signatures of each type of adversity, characterization of temporally and spatially specific epigenetic responses to adversity, and elucidation of the biological processes affected by these signatures (Murgatroyd & Spengler, 2011). Critical and sensitive periods have been proposed for various stressors, including maternal care and environmental enrichment, and the timing of repeated stressors (chronic stress) during these neurodevelopmental windows is critical for determining the nature of the epigenetic program accumulated and the extent to which a permanent mark is left on the organism. Even

stressors not considered traumatic, such as changes in child-care provider frequency or brief separations from primary caregivers, can elicit temporally defined epigenetic modifications that influence the behavioral response to a future trauma. Opposing epigenetic marks can also be placed at the same chromosomal locus by different environmental signals at specific times, allowing for the encoding of independent environmental exposures. These interactions between early-life influences can shape the architecture of the genome to impart vulnerability as well as resilience to subsequent disorders.

Timing, Dose, and Type of Early Adversity

Adverse experiences during early development can profoundly increase the risk of stress-related disorders across the lifespan. While the intensity and number of such experiences are critical factors, the type of stressor and its timing relative to developmental windows of heightened plasticity also significantly influence how the stress response becomes dysregulated and how stress-related psychopathology is expressed later in life (C. Jawahar et al., 2015). The importance of exposure to excess stress during early development is widely acknowledged. There is also important variation in the timing of such exposures during the early years. Most theorists identify a first sensitive period during prenatal development encompassing both maternal stress and environmental conditions influencing fetal stress exposure. A second sensitive period spans the first 18 to 36 months postnatally, during which wide-ranging attachments to caregivers and self-regulatory skills emerge. A third sensitive period is the preadolescent transition to puberty; during this period, the expanding social world presents novel hazards.

Sex Differences and Moderating Variables

Assorted evidence indicates males are more vulnerable to psychotic disorders, whereas females are more likely to develop anxiety, trauma-related, and stress-related disorders (Jaric et al., 2019). Biological sex influences the neurobehavioral sequelae (i.e., hyper-responsiveness and hypo-responsiveness) of adolescent stress, the responsiveness to preventive interventions, and the formative nature of stress during puberty. Sex differences appear to be especially pronounced in conditions with greater genetic heritability (e.g., schizophrenia) and females are unaffected when the genetic contribution to a disorder is minimal. The effects of conditioning and chronic stress on subsequent acquisition and extinction of fear responses differ in males and females. Males and females also respond differently to early social isolation stress. Adolescent cocaine-induced behavioral sensitization differs between males and females and is further influenced by stress. Females exposed to infantile stimulation during social isolation show fewer adult behavioral disturbances compared to untreated males, indicating the importance of early life experiences. Estrogen, progesterone, and testosterone modulate endocrine and physiological responses to acute stress beyond the organizational and activational effects of sex hormones. Sex-specific stress responses, including the glucocorticoid stress response in the HPA axis and the control of nutritional signals on energy availability, are influenced by the presence of estrogen. Females differ from males in the mediation of the relationship between early life stress, epigenetic programming, and adult emotional regulation, leading to increased susceptibility to stress disorders (Abdurakhmanov, J., et al).

Methodological Considerations in Epigenetic Research

The potential of early life stress (ELS) to increase vulnerability to stress-related psychiatric disorders is well established. Emerging epigenetic evidence indicates that stressful early experiences may lead to stable modifications of the epigenetic signature of stress-regulating genes. Significant changes in DNA methylation and histone modification patterns associated with ELS have been reported for several stress-regulating genes and their transcriptional variants in animals. Correlative human studies observed similar ELS-related alterations in DNA methylation patterns at stress-regulating genes and gene transcription variants in blood samples from adolescents and young adults. Such alterations can be reliably measured and have been additionally linked to clinically established endophenotypes of stress-related psychopathology (Sasmakov, S. A., et al).

Different-epigenetic, pharmacological, and observational-approaches suggest that the programmatic impact of ELS on gene transcription and corresponding stress-regulating systems may occur during early development and is shaped by emotional regulatory capacity. Building on existing conceptual models of developmental psychopathology, the specific programming effects of ELS on stress-related psychopathological trajectories were examined across the entire developmental period from infancy through old age (Ziyaev, A. A., et al). The analysis further highlights critical and sensitive periods as well as dosage, type, and sex differences of early adversities as central moderators of this programming. Knowledge of the timing, dose, and nature of the programming impact of ELS on gene transcription and stress-related systems offers potential avenues for novel intervention and prevention strategies targeting underlying epigenetic signatures and gene-regulatory architecture (C. Jawahar et al., 2015).

Study Designs and Measuring Early Life Stress

Measurement of early life stress (ELS) is a fundamental methodological issue in epigenetic studies aiming to identify ELS-responsive markers, given the variety of exposure types, timing, and the disparities between subjective perception of stress and observable exposure. Various strategies have been developed to characterize early adversities based on different criteria, such as prevalence, severity, and biological impact, in order to attain a better established and more consistent characterization of the numerous and diverse types of ELS. Factors such as exposure to maltreatment, substance abuse by the mother, hostility or violence within the family, and parental divorce have been among the most analyzed indicators of ELS (C. Jawahar et al., 2015).

Considerable efforts to characterize and retain the complexity of the context-specific nature of ELS comprise among the most advanced study designs and indices, such as quantitative indices and mixed measures integrating exposure type and poly-victimization scores, sensitive-period ratings, qualitative coding of video observations of maternal–newborn interactions, and videotaped family environments scaled for risk (K. Short et al., 2023). A similar concern to delineate the prenatal to postnatal transition can be observed in the development of indicators of ELS that characterize exposure either during pregnancy or the first year of life, based on a sound theoretical framework that takes into account the significant neurobiological changes during this critical period of development. Such careful consideration of timing, context, and theory provides specifications of ELS characteristics amenable to computational modeling of biological events, enhancing the robustness of biomarkers that are sought for a better understanding of the association between stress and the development of psychopathology.

Epigenetic Assays and Tissue Specificity

Early life stress (ELS) enhances vulnerability to stress-related psychopathologies in adulthood. It is well established that ELS increases the risk of diverse psychological disorders and that epigenetic mechanisms mediate the long-lasting impact of early stress. Epigenetic changes triggered by ELS are tissue- and time-specific, pointing to an epigenetic signature of ELS that mirrors the timing of the stressor. Epigenetic changes in response to ELS have been observed in various tissues, including blood, saliva, and hair follicles, offering opportunities to study ELS in easily accessible peripheral tissues. ELS-induced epigenetic alterations include DNA methylation changes, histone modifications, and non-coding RNAs involved in the regulation of HPA axis activity, stress hormones, and neuroplasticity. These changes occur in genes relevant to the stress response, emotional regulation, and developmental plasticity.

Although investigations of ELS in peripheral tissues have utilized diverse methodologies, sensitive and specific biomarkers are still lacking. Early stress can be measured in animal models, but corresponding measurements in patients are more problematic. Techniques such as cross-species bioinformatics, micro-RNA profiling, and inference of transcription factor binding sites from long non-coding RNA expression data have been employed to identify epigenetic signatures associated with ELS. Current epigenetic assays can distinguish between early-life and adult stress, stress reactivity and recovery, and chronic versus acute stress. These developments open pathways for more targeted biomarker discovery (C. Jawahar et al., 2015).

Causality, Replication, and Longitudinal Approaches

The evidence cited above supports a multifactorial role of ELS on ER and highlights the need for more longitudinal studies assessing the timing of ELS and its long-term consequences on the risk of stress-related psychopathology. Several methodological considerations require further attention.

Causal relations between stress, epigenetic markers and psychopathology remain to be established. In most studies, markers were analyzed only at one moment in time, impeding the inference of a causal network. The observation of ELS epigenetic modulation accompanied by changes in ER, in-turn modifications of stress responsivity and emergence of different psychopathological traits across development provide piece of evidence supportive of such pathway (C. Jawahar et al., 2015). Direct experimental designs manipulating ELS are also needed (Azimova, S., et al. 2023).

Translational Implications and Intervention Strategies

The variation in susceptibility to stress-related psychopathology highlighted distinct biomolecular process tracking exposure to different types of early adversity. Numerous preclinical and clinical studies have identified a consistent set of epigenetic markers associated with early life stress at the molecular level, indicating that epigenetic alterations may serve as biological signatures of early adversity and facilitate the understanding of the mechanisms linking early life stress to psychopathological outcomes and emotional-regulation difficulties. Such biomarkers may advance risk-stratification efforts and serve as endpoints for monitoring intervention efficacy (C. Jawahar et al., 2015).

The ideal situation for successful aetiological treatments would involve prevention of exposure to any type of early-life adversity, especially during sensitive periods of development. However, this is not practically feasible. Thus, a complementary approach involving the co-influence of early-life stress moderation via epigenetic programs together with early intervention is to consider intervention programs specifically designed to counterbalance the consequences and resultant alterations induced by early adversity (Ziyaev, A. A., et al). Such biological pathway-modulating therapies could be the consideration of novel, epigenetic-informed strategies addressing at-risk individuals exposed not only to adversity but even more broadly, early stress modulators such as the provision of enriched home, school, or community environments combined with routine assessments of epigenetic markers (Sasmakov, S. A., et al).

Furthermore, from an ethical perspective, adoption of a preventive focus from the earliest, harmless stress-specific tracers raising the issue of permanent tags requires regulatory policies to determine permissible investigational ranges and lengths or measures of permissible avoidable stress variables, as exposure would afford opportunity to investigate genetic and epigenetic interaction patterns in multiple tissues (Joachim Raabe & Spengler, 2013).

Biomarker Potential for Risk Stratification

Many patients suffering from 'stress-related' psychiatric disorders experienced traumatic or aversive childhood experiences and stressful life events before onset of their illness. Early-life stress alters the trajectory of brain development and behaviour, thereby increasing susceptibility to develop psychopathological symptoms in adulthood (K. Short et al., 2023). Depression/anxiety and alcohol abuse contribute to elevated early externalising behaviours, which are significant predictors of later substance use in adolescent anger-based pathways. Affective disorders, e.g. major depressive disorder (MDD) and anxiety disorder, are among the most common and debilitating mental illnesses considered early-life stress (ELS) important environmental determinant of their onset, persistence and recurrence for modulating subsequent development (C. Jawahar et al., 2015). Thus, investigation of early adversities and mechanism underlying

how stress responses on individual psychiatric symptoms during sensitive developmental episodes may provide more precise intervention of early-life stress exposure to prevent further development of psychopathology later in life (Abdurakhmanov, J., et al).

Epigenetic-Informed Interventions and Prevention

Epigenetic-informed interventions and prevention. The presence of epigenetic signatures in biological systems provides insight into the mechanisms via which early adversity programs psychopathological risk across the lifespan and allows the identification of precise critical/sensitive windows, or time intervals post-stressor exposure, during which interventions might prevent or mitigate the onset of stress-related disorders (C. Antonelli et al., 2022). Early life stress is associated with alterations in DNA methylation and histone modifications in several genes implicated in the hormonal, neural, and molecular pathways regulating the stress response and contributing to emotional behaviour (C. Jawahar et al., 2015). Targeting these epigenetic modifications or the neurobiological processes with which they engage could thus inform intervention strategies that take into consideration the specific type of early stress experienced (i.e., high versus low threat) and the emotional regulation strategy that has been adopted (adaptive versus maladaptive). Knowledge of epigenetic signatures can also facilitate the development of early screening tools by offering the possibility of establishing a clear link between the nature of stressful experiences and the biological sequelae associated with them. Children exposed to prenatal adversities, for instance, display well-characterised epigenetic alterations of the glucocorticoid receptor gene. Assessment of these changes may therefore help identify pregnant women whose infants will be at heightened risk of neurodevelopmental issues (Azimova, S., et al. 2023).

Targeted prevention initiatives are particularly important for individuals underscoring an extensive risk profile due to multiple, potentially synergistic early life stressors. Nevertheless, genetic and epigenetic markers do not yet serve as predictive biomarkers of stress-related disorders. Longitudinal research is required to establish whether the epigenetic modifications observed after early adversity and the neurobiological circuits affected remain associated with a greater vulnerability to psychopathology later in life (Ruzibaeva N., et al).

Ethical and Policy Considerations

The epigenetics of early life stress (ELS) has gained attention due to increasing evidence linking exposure to adverse experiences during sensitive developmental windows to long-term alterations in brain function, increased vulnerability to mood and anxiety disorders, and risk of other pathologies. These effects suggest epigenetic modification may represent a significant mechanism through which the environment influences health and disease. ELS-induced epigenetic changes that have been consistently observed across species involve DNA methylation, histone modification, and the activity of non-coding RNAs, all of which play important roles in the regulation of genes that are recognized as key endpoints in stress-response pathways. ELS is reported to significantly impact the epigenome during transcriptionally active peri-conception stages (C. Jawahar et al., 2015). Importantly, gene regulatory mechanisms triggered by ELS operate in a programmatic manner to affect different groups of genes at various stages of development. The timing, type, and dose of ELS experienced by the organism shape the nature of the regulatory responses and alter cells, circuits, and the development of vulnerability to stress-related psychopathologies in a target-dependent manner (Allabergenov M., et al).

Neurobiological mechanisms are emerging to explain how early exposure to adverse experiences might get anchored epigenetically in the developing organism and causally influence the emergence of a well-characterized range of stress-related pathologies. In the context of ELS, epigenetic modifications are proposed to engage distinct coupling mechanisms that connect the external world with internal cellular configurations. Expression of the appropriate set of candidate genes further engages sets of coregulated, conditionally selected, and imprinted genes whose products influence the development of stress-related

pathology through their actions on well-characterized cellular endophenotypes across neurobiological circuits known to underlie affective and cognitive features of the same disorders (Ochi & Dwivedi, 2023).

Future Directions

Exposure to stressors near birth can alter gene expression through epigenetic mechanisms, resulting in long-term changes to the stress response system. Evidence suggests that exposure to early life stress can induce epigenetic changes, predisposing individuals to poor stress regulation later in life. Robust evidence links early-life stress to the development of trauma-related disorders and deleterious alterations in emotional regulation. Changes in DNA methylation, histone modifications, RNA profiling, chromatin remodelling, and small RNA packaging, distribution, and biogenesis have all been shown to occur in response to early-life stress and are coordinated by epigenetic mediators such as sirtuins, histone deacetylases, and serotonin reuptake in mammals. The transcription of stress-responsive genes, including BDNF and GR, is regulated in a spatiotemporal manner across core regions of the stress response circuitry, including the hypothalamus, bed nucleus of the stria terminalis, amygdala, and prefrontal cortex (Azimova, S., et al. 2023). Ongoing work seeks to extend cross-species correlative findings towards understanding the mechanisms underlying the programming of stress- and adversity-related pathology across the lifespan. Furthermore, the translation of rodent models into human studies continues to reveal parallels in both proximal epigenetic programming and distal functional outcomes (Sasmakov, S. A., et al). Such convergent approaches further elucidate the role of epigenetic programming in the impact of early life adversity on the trajectory of the stress response. Work across rodent models continues to identify gene orchestrators and broad regulatory networks controlling epigenetic remodeling and transcriptional regulation. Further work is required to determine the extent to which rodent epigenetic signatures and associated functional circuitry modifications extend to the human condition. Determining whether existent human signatures are complements or elaborations of these core rodent sites remains critically important (Mannonov A. et al).

Conclusion

Early-life stress developmentally programs an increase in the risk for psychopathology. Epigenetic alterations, triggered by the experience of early adversity, constitute an effective pathway through which the environment can shape the genome. Evidence indicates that epigenetic changes accompanying early-life stress influence circuits that underlie emotional regulation, a key mediator in the development of stress-related psychological disorders. Epigenetic regulation of emotional states has been observed at multiple temporal phases following the occurrence of early-life stress. Experimental research with laboratory animals identifies the social neglect paradigm as a powerful model of stress and trauma to investigate epigenetic reprogramming. During this stressful experience, genetic information remains unaltered, while epigenetic changes are evident in numerous stress-responsive genes, providing valuable avenues to identify human homologs that may be similarly affected. Understanding the mechanisms by which early-life adversity alters the neurodevelopmental trajectory and increases the risk for stress-related psychopathology is of utmost importance for the advancement of mental health research.

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