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Review Article

Epigenetic embedding of childhood adversity: Linking adverse childhood experiences to addiction

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Abstract: Adverse childhood experiences shape the developing brain in ways that increase vulnerability to substance use across the lifespan. This review brings together evidence from epigenetics, neuroscience and forensic psychology to explain how early stress becomes biologically embedded. Childhood adversity alters patterns of DNA methylation in genes that regulate stress response, neuroplasticity and reward processing, including NR3C1, FKBP5, BDNF, DRD2 and OPRM1. These molecular changes heighten sensitivity to stress, weaken the capacity to experience pleasure and increase impulsive behavior. As a result, substance use often emerges as an attempt to cope with an internal environment marked by emotional and physiological dysregulation. Repeated substance use then reinforces the same biological pathways, creating a cycle that is difficult to break. Research from different countries shows a clear association between adversity, epigenetic variation and accelerated biological aging. While direct causal evidence in humans is still emerging, statistical models and animal studies suggest a potential basis for the intergenerational transmission of trauma-related susceptibility. Studies from Türkiye report strong links between childhood trauma, dissociation and substance use, although molecular research remains limited. Interpreting these findings through a forensic lens highlights the need to move beyond purely punitive views of addiction. Trauma and biologically informed approach can support more effective prevention, treatment and rehabilitation strategies.

Keywords: Child Abuse, Early Life Stress, Addiction, Epigenetics, Forensic Psychology.

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Introduction

The integration of a forensic psychology perspective into the study of Adverse Childhood Experiences (ACEs) and Substance Use Disorder (SUD) is critical for translating molecular findings into actionable justice and rehabilitation frameworks. While epigenetics illuminates the "biological embedding" of trauma, explaining how early adversity alters gene expression related to impulse control, aggression, and stress regulation also it is the forensic psychological/psychiatric lens that contextualizes these biological adaptations within the realms of criminal responsibility, culpability, and recidivism risk. Merging epigenetic evidence with psychological assessment is essential not to advocate for biological determinism, but to construct a robust bio-psycho-social model that challenges traditional punitive approaches by presenting addiction as a physiological adaptation rather than a mere moral failing.

This review allows practitioners to better understand the etiology of harmful behaviors and supports the development of trauma-informed sentencing and rehabilitation strategies that leverage the potential for epigenetic reversibility.

Adverse Childhood Experiences to Substance Use

The causal relationship between the psychosocial stress caused by ACEs and SUD is explained by a complex process of "biological embedding" governed by epigenetic mechanisms (Boyce et al., 2012; Ngo et al., 2025). Although chronic early-life stress does not alter the DNA sequence itself, it reprograms the methylation patterns regulating gene expression, creating a neurobiological "priming" ground (Zang et al., 2023). Specifically, hypermethylation of the *NR3C1* gene, which modulates the stress response, renders the HPA axis hypersensitive, while epigenetic alterations in the *DRD2* and *OPRM1* genes within the reward system blunt the individual's capacity for pleasure (anhedonia) (Misiak et al., 2021; Peña et al., 2019). This molecular landscape leaves the individual vulnerable to external stressors and internally suffering from "reward deficiency." Consequently, substance use in these individuals emerges not as an arbitrary choice, but as an attempt to artificially balance an epigenetically dysregulated neurobiology or as a maladaptive coping strategy (Jordan & Andersen, 2017).

In a cycle, the substances themselves (alcohol, opioids, etc.) imprint their own epigenetic signatures, perpetuating the impairment in the brain's reward and stress pathways and locking in the cycle of addiction (Casiano, 2025).

International Empiric Findings

Quantitative research from international literature highlights significant correlations between early adversity and epigenetic markers (such as DNA methylation and Epigenetic Age Acceleration) that predispose individuals to substance use. A systematic review and meta-analysis of candidate gene studies estimated the overall correlation coefficient between childhood adversity and DNA methylation variation at $r = 0.291$ ($p < 0.001$). This statistically confirms that early life stress significantly predicts variations in the epigenome, particularly in systems regulating stress and immunity (Neves et al., 2021). Longitudinal data indicates a dose-response relationship between ACEs and biological aging. Individuals with 4 or more ACEs demonstrated significant epigenetic age acceleration (EAA) compared to those with fewer adversities. Specifically, at age 20, the Extrinsic Epigenetic Age Acceleration (EEAA) was increased by $\beta = 1.05$ years (95% CI [0.66, 1.44]), and GrimAge acceleration was increased by $\beta = 0.57$ years (95% CI [0.28, 0.87]) (Raffington et al., 2021). Even lower exposure levels (1–2 ACEs) were associated with an acceleration of 0.86 years (Horvath units) (95% CI [0.29, 1.43], $p = 0.003$) compared to individuals with zero ACEs (Bayer et al., 2023).

Substance use itself accelerates epigenetic aging, compounding the effects of trauma. A longitudinal study found that weekly cannabis use from adolescence to adulthood was strongly associated with accelerated DNA methylation aging ($\beta = 1.665$, SE = 0.591, $p = .005$). The cumulative exposure to

mental health symptoms, substance use, and early adversities was associated with an accelerated aging effect of approximately 3.17 to 3.76 years (Lawn et al., 2023). Statistical modeling has shown that the effect of maternal ACEs on neonatal *COMT* gene methylation (a gene involved in dopamine degradation) is 64% mediated by the mother's own *COMT* methylation patterns (Indirect effect: $p = 0.044$, 95% CI [0.0025, 0.32]). This suggests a statistical basis for the biological transmission of trauma susceptibility across generations (Mohazzab-Hosseinian et al., 2023).

Empiric Findings from Türkiye

While epigenetic research in Türkiye is still developing compared to Western literature, recent studies provide strong clinical and preliminary statistics regarding the link between childhood trauma and substance use.

In a study of 133 individuals with substance use disorders in Türkiye, participants scored highest on the Emotional Neglect subscale of the Childhood Trauma Questionnaire (CTQ), with a mean score of 12.83 ± 3.46. This study statistically linked these traumatic experiences to dysfunctional coping mechanisms such as "behavioral disengagement" and "denial" (Orak et al., 2023). Again, a descriptive study involving 173 substance-dependent individuals in Eastern Türkiye reported a total mean CTQ score of 34.8 9± 14.19. The study found a significant, albeit weak, positive correlation ($p < .05$) between dissociative experiences (a psychological detachment often linked to biological stress dysregulation) and types of abuse, particularly emotional and physical abuse (Aktas et al., 2024).

To best of our knowledge there is one molecular study conducted in Türkiye regarding this topic. A molecular study conducted by Yilmaz et al. (2021) on Turkish adolescents with suicide attempts (a group with high ACE prevalence) examined Brain-Derived Neurotrophic Factor (BDNF) gene expression from whole blood samples. Although the study found significantly higher CTQ scores in the case group compared to controls, it reported no statistically significant difference in BDNF gene expression levels between the groups ($p > 0.05$). This "negative" finding is crucial as it suggests that biological embedding in the Turkish population might manifest through more complex, tissue-specific epigenetic mechanisms rather than simple gene expression levels in blood, or that resilience factors specific to the culture might be buffering certain biological effects.

Although Yılmaz et al. (2021) reported no statistically significant difference in *BDNF* gene expression between the trauma-exposed group and controls, this "negative" finding warrants a nuanced interpretation regarding tissue specificity and resilience. It is well-documented that peripheral blood *BDNF* levels do not always linearly reflect brain tissue concentrations, particularly under complex stress conditions (Klein et al., 2011). While blood *BDNF* is often used as a proxy, it is influenced by platelet activation and peripheral inflammation, which may mask central nervous system downregulation in some clinical populations.

The integration of epigenetic evidence into forensic psychology compels a re-evaluation of traditional concepts regarding criminal responsibility and rehabilitation. Unlike fixed genetic mutations, epigenetic modifications—such as the methylation of *NR3C1* or *BDNF*—are dynamic and potentially reversible, representing a "biological scar" of environmental trauma rather than an immutable character flaw. This distinction is critical for forensic risk assessment; it suggests that the impulsivity and emotional dysregulation seen in offenders with a history of ACEs may be driven by a treatable physiological adaptation (Gerra et al., 2024; Mustafin et al., 2019). Consequently, the legal system's focus could shift from purely punitive measures to "epigenetic rehabilitation," where trauma-informed interventions aim to reverse these maladaptive markers. Thus, acknowledging epigenetic reversibility supports a restorative justice model, framing addiction and recidivism not merely as moral failures but as biological cycles that can be

broken with appropriate environmental and clinical remediation.

Allostatic Load

When examined through the lens of social science, early life stress is not merely a psychological trauma but a process wherein social disadvantages are inscribed onto the body. The concept of allostatic load, named by Bruce McEwen, defines the cumulative cost exerted by chronic stress; when an organism is compelled to persistently activate stress response systems (such as the HPA axis) to adapt to environmental challenges, this physiological "wear and tear" precipitates systemic dysregulation and accelerated aging. Epidemiological data underscore the tangibility of this burden; for instance, a study conducted by Slopen et al. (2014) determined that a one-standard-deviation increase in childhood adversity scores was associated with a 9% increase in cumulative biological risk (allostatic load) in adulthood (Incident Rate Ratio = 1.09). Similarly, a large-scale analysis utilizing UK Biobank data statistically demonstrated that each additional adverse childhood experience reported by female participants resulted in a 4% increase in allostatic load (Jakubowski et al., 2023). As elucidated by Arline Geronimus's "weathering hypothesis," this phenomenon serves as evidence that exposure to structural inequalities and systemic stressors accelerate biological aging processes, confirming that health disparities are not merely genetic outcomes but rather the biological residue of lived social experiences.

Exposure to ACEs, including forms like childhood sexual abuse (CSA), is strongly associated with an increased susceptibility to psychiatric diagnoses such as substance use disorders (SUDs) and food addiction (FA) later in life (Wiss et al., 2021). The stress resulting from early life adversity (ELA) generates neurobiological changes, disrupting the circuits responsible for regulating stress response, neuroplasticity, and reward, thereby conferring heightened vulnerability to addictive behaviors (Wiss et al., 2021; Zarse et al., 2019). The overlap between neurobiological changes seen in SUDs and FA further supports the notion that addiction-like eating may serve as a mechanism of self-medication following trauma (Brewerton, 2011; Wiss et al., 2021).

HPA Axis and Stress Response

A major mechanism linking ACEs to addiction susceptibility involves epigenetic modifications of genes related to the Hypothalamic-Pituitary-Adrenal (HPA) axis (Wiss et al., 2021). The HPA axis, which regulates the body's stress response, utilizes the Glucocorticoid Receptor (GR), encoded by the NR3C1 gene, as a critical component of its negative feedback loop (Forum et al., 2025; Khan et al., 2025). Early adversity exposure is linked to altered NR3C1 DNA methylation levels in peripheral cells, which, in turn, has been associated with the development of depressive, anxiety, and SUD in adulthood (Tyrka et al., 2016). Specifically, individuals with a past substance-use disorder diagnosis demonstrated lower levels of DNA methylation in the NR3C1 gene promoter compared to unexposed, healthy controls (Tyrka et al., 2016). Similarly, the FKBP5 gene, which regulates GR activity, exhibits epigenetic changes following stress that are critical to trauma-related disorders like post-traumatic stress disorder (PTSD), a condition highly comorbid with SUDs (Khan et al., 2025; Zannas et al., 2016).

Furthermore, addiction vulnerability influenced by ACEs involves disruption in neurotrophic and reward systems. Brain-Derived Neurotrophic Factor (BDNF) and its receptor, Tropomyosin receptor kinase B (TrkB), which are vital for synaptic plasticity, are impacted by the epigenetic embedding of early stress (Wiss et al., 2021; Vyas et al., 2023). For example, adolescent exposure to alcohol in animal models results in altered epigenetic marks at the *Bdnf4* promoter, leading to decreased transcription and contributing to increased adult susceptibility to SUD (Bohnsack et al., 2022; Kyzar et al., 2019). The dopamine system, central to reward, is also vulnerable: alterations following Early Life Adversity increase impulsive behaviors, which fuel addiction

(Wiss et al., 2021). In functional magnetic resonance imaging (fMRI) studies, Food Addiction (FA) is acknowledged to share neurobiological similarities with SUDs (Schulte et al., 2016; Wiss et al., 2021), often demonstrating reduced cortico-basal ganglia reward sensitivity resulting from inflammation precipitated by ELA (Wiss et al., 2021).

Other receptor systems crucial to stress and behavioral regulation are epigenetically modulated by ACEs, cementing the connection to addiction. Changes in methylation status have been identified in the gene for the serotonin transporter, SLC6A4, following childhood trauma, which is associated with depressive, anxiety, and substance-use disorders (Koenen et al., 2011; Tyrka et al., 2016). Additionally, the opioid pathway is influenced, as evidenced by epigenetic changes in the Kappa opioid receptor (OPRK1) gene observed in suicide victims with a history of child abuse (Lutz et al., 2018; Neves et al., 2021). These disruptions establish biological pathways through which early trauma directly predisposes individuals to addiction, whether through substance abuse or addictive-like eating behaviors, suggesting that addressing the biological consequences of ACEs is necessary for effective recovery (Wiss et al., 2021).

ACEs on Dopaminergic and Opioid Receptor Systems

The influence of ACEs on the dopaminergic (DRD) and opioid (OPRM) receptor systems provides crucial insight into the neurobiological mechanisms underlying increased vulnerability to addiction, including both substance use disorders (SUDs) and food addiction (FA) (Wiss et al., 2021). Disruptions caused by early life adversity (ELA) lead to permanent changes in the brain's reward circuitry, a process known as biological embedding (Wiss et al., 2021). Alterations in the dopamine system specifically are linked to increased impulsive behaviors, which are a major risk factor for developing addictions (Wiss et al., 2021). This vulnerability stems from epigenetic modifications that affect the transcription and expression of dopamine receptors. For example, research examining women exposed to childhood sexual abuse compounded with bulimia spectrum disorder identified hyper-methylation of the Dopamine D2 receptor (DRD2) gene (Groleau et al., 2014; Neves et al., 2021). Furthermore, preclinical models highlight how early-life environment and substance exposure can epigenetically program these receptors; gestational exposure to substances like THC was linked to a decreased density of DRD2 receptors in the nucleus accumbens (NAc) of adult offspring due to an increase in repressive epigenetic marks at the *Drd2* gene (Dinieri et al., 2011; Liu et al., 2024; Sadeghzadeh et al., 2017). The functional implications of these receptor changes are complex and cell-type specific, as overexpression of microRNA-1 (miRNA-1) in D1-containing neurons increased cocaine self-administration (SA) seeking, while overexpression in D2-containing neurons resulted in a reduction of cocaine SA in animal models (Forget et al., 2021; Liu et al., 2024).

The opioid system, mediated through opioid receptors such as the Mu Opioid Receptor (MOR) and Kappa Opioid Receptor (OPRK1), is also critically affected by early life stress and contributes to addiction pathways. Chronic stress has been shown to increase susceptibility to Food Addiction (FA) by increasing the levels of MOR (Liu et al., 2019; Wiss et al., 2021). Moreover, the consumption of highly palatable foods, which is associated with FA and often follows ACE exposure, has been shown to cause endogenous opioid dependence and activate reward areas of the brain in a manner similar to opiates (Colantuoni et al., 2002; Spangler et al., 2004). It is important to note that data on Food Addiction (FA) are presented in this review specifically as a neurobiological model. Given the shared reward circuitry dysfunctions and cross-sensitization observed between FA and Substance Use Disorders (SUDs), these findings offer critical insights into how early adversity disrupts dopaminergic and opioid signaling, regardless of the specific addictive agent.

The gene encoding the Kappa opioid receptor, *OPRK1*, has been specifically linked to trauma-

related pathology. Studies analyzing brain tissue (anterior insula) of suicide victims with a history of child sexual and physical abuse found hypo-methylation of intron 2 in the Kappa variant 1 region (Lutz et al., 2018; Neves et al., 2021). This epigenetic modification was associated with decreased kappa expression (Lutz et al., 2018; Neves et al., 2021). Additionally, chronic stress exposure in adulthood can sensitize an individual's response to opioids, enhancing drug preference behaviors like morphine-conditioned place preference (CPP) via alterations in glucocorticoid receptor (GR)-mediated epigenetic regulation (Chen et al., 2019; Liu et al., 2024). This interplay between the stress response (GR signaling) and opioid pathways highlights how ACEs create a long-lasting biological vulnerability that predisposes individuals to both opioid substance use and addictive eating behaviors.

Conclusion

To sum up, the convergence of molecular genetics and social epidemiology compels a fundamental paradigm shift in how we understand the trajectory from ACEs to addiction. The evidence reviewed herein demonstrates that the "social" and the "biological" are not distinct spheres; rather, through epigenetic mechanisms and allostatic load, social adversity is transmuted into physiological vulnerability. The dysregulation of the HPA axis and reward circuitry manifested in the methylation of genes such as NR3C1, BDNF, and DRD2, confirms that addiction is often less a failure of will than a biological embedding of survival in a toxic environment. Consequently, the forensic and justice systems must move beyond a purely punitive framework. Acknowledging that the "scars" of inequality are written into the genome necessitates a restorative approach. Crucially, unlike genetic mutations, epigenetic marks are dynamic and potentially reversible. Therefore, legal and clinical interventions should be designed not merely to correct behavior, but to leverage this reversibility through trauma-informed rehabilitation strategies.

Ultimately, we recommend the standardization of trauma-informed assessment processes within the judicial system to better identify these biological vulnerabilities. Preventing the intergenerational cycle of addiction requires treating the social conditions that trigger these epigenetic modifications, recognizing that the most effective neurobiological intervention is often a safe and nurturing environment.

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Ethical Declaration

Since this study is a review article, ethics committee approval is not required, and the Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: MAE, Design: MAE, Supervising: MAE, Financing and equipment: MAE, Data collection and entry: MAE, Analysis and interpretation: MAE, Literature search: MAE, Writing: MAE, Critical review: MAE

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