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Developmental Stage Epigenetic Modifications and Clinical Symptoms Associated with the Trauma and Stress of Enslavement and Institutionalized Racism

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Abstract

The large-scale capture, forcible kidnapping, and subsequent forced labor associated with the historic enslavement of Africans in the Americas exerted tremendous stress on their biologies. These stresses provided the most important substrate for selection in New World African populations. The environmental and social conditions of enslavement, post-civil war reconstruction, and Jim Crow racism in the United States were a connected sequence of traumatic events that have had an enduring, multigenerational impact on African Americans and their descendants. Enslavement is manifested partially in elevated cortisol levels and, in turn, have served as catalysts for other adverse health outcomes. Elevations in circulating cortisol levels have been indicated as a significant influencing factor in psychological stress disorders such as depression and post-traumatic stress disorder. Stress responses were reinforced no doubt by the long-term food insecurity associated with enslavement. Chronic food deprivation and food instability are thought to have further exacerbated the trauma associated with other adversarial environmental effects during this period. The impact of these constraints during key stages of the lifecycle are examined and the resulting clinical symptoms and epigenetic changes documented.

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Background

Capture, extensive migration, torture, forced labor, and detribalization exerted tremendous stress on the biology of enslaved Africans and severely taxed their abilities to remediate effectively. The likely epigenetic effects were so dramatic as to modify the directionality of ancestral trajectories in the surviving descendants of these Africans. In other words, enslavement in the Americas and its sequelae produced a wide assortment of new and powerful selective pressures on kidnapped and enslaved Africans. Under these conditions, old responses that had been effective in the African context may have been less advantageous and even disadvantageous in the American context. Each step in the enslavement process exerted its unique cluster of effects on the biology of enslaved individuals at specific stages in the lifecycle.

Kidnapping and extensive migration within Africa took its toll on targeted individuals and groups; torture and forced labor required new responses to ensure survival. In the Americas, detribalization coupled with wide-scale color-based racial discrimination forced new realities on the enslaved. The biological effects of these traumatic events can be grouped into three broad categories. First, there were immediate changes in the epigenome, which arose from the forced movement of African individuals to a novel environment in the Americas. Second, there were biological effects due to the trauma associated with enslavement and its maintenance. The persistence of these environmental conditions stimulated chronic epigenomic alterations. Finally, there were those biological consequences due to institutionalized racial discrimination, violence, social disenfranchisement, and Jim Crow segregation – the American apartheid that persisted in the centuries after emancipation. These further entrenched multigenerational changes in the epigenome.

Impacts on Developmental Stages in the Life Cycle

Whipping, shackling, beating, mutilation, branding, amputations,

sexual exploitation, and imprisonment have left their marks. The punishment associated with enslavement and protracted racism was meted out most often in response to disobedience or perceived infractions, but slave owners and overseers abused slaves arbitrarily as an assertion of their dominance [1-3]. In addition to physical injury caused by beating, the enslaved suffered from chronic conditions caused by overwork, scanty rations, skimpy clothing, and exposure due to inadequate housing. Pregnancy was not a barrier to punishment; methods were devised to administer beatings without ostensibly harming the fetus.

Prenatal epigenetic effects

Severe early life stress as well as exposure to social discrimination can be toxic to later mental and physical health [4,5]. During the centuries of American Slavery, no age group of enslaved African Americans was exempt from the stress of bondage; the specific epigenetic effects varied according to life phase. Empirical research from Holocaust survivors supports the view that parental trauma or stress exposure can have a direct biological impact on offspring [6]; it provided as well a context for intergenerational transmission of insult via epigenetic modification of gametes and modification of the gestational uterine environment. Exposure to stress early in life has been reported permanently to alter the activity of the hypothalamic-pituitary-adrenocortical (HPA) axis and the brain in general [7]. While chronic stress fosters disease presumably by activating the hypothalamic-pituitary-adrenocortical (HPA) axis, the research linking chronic stress and HPA function is somewhat contradictory. Some studies report increased activation, and others report the opposite. However, a recent meta-analysis showed that much of the variability is attributable to the nature of the stressor and to idiosyncratic features. Timing of the stressor appears to be an especially critical element, as hormonal activity is elevated at stressor onset but reduces as time passes [8]. Stressors that threaten physical integrity, involve trauma, and are uncontrollable elicit a high, flat diurnal profile of cortisol secretion [8]. Ultimately, however HPA activity is shaped by individual's response to the situation; reportedly, it increases with subjective distress but is lower in persons with posttraumatic stress disorder.

Enslaved pregnant women carried their pregnancies knowing that they could be separated from their newborn at any time by the capricious dictates of slave owners. They may be forced to provide their breast milk for the slave owner's family, and that they were expected to fulfill work quotas right up to the week or even day of delivery. Some pregnancies in enslaved women were the result of rapes by slave owners and overseers, while other pregnancies were the product of forced copulations with other slaves.

Most infants were weaned early, within three or four months of birth. Then, they were fed gruel or porridge made of protein-poor cornmeal; this increased the child's potential to develop kwashiorkor, rickets, and pellagra. Surely being enslaved and pregnant took its toll on the fetus in high rates of infant mortality. Historian Steven Mintz [9] reports that infant and child mortality rates were twice as high among enslaved children as among southern European-American children. This pattern during slavery may still affect contemporary Legacy African American infant mortality rates [10]. A significant contributor to the high infant and child death rate during slavery was chronic undernourishment. Slave-owners showed little concern for enslaved mothers' health or diet during pregnancy. Pregnant women were not provided any extra rations and were employed in intensive fieldwork even in the last week before they gave birth. Not surprisingly, enslaved mothers suffered high rates of spontaneous abortions, stillbirths, and deaths shortly after birth. Half of all enslaved infants weighed less than 5.5 pounds (2.49476 kilograms) at birth. Today, this is considered severely underweight.

The mother's condition has a direct bearing on the health of the newborn. Glucocorticoids pass through the placenta to the fetus. This means that some postnatal impacts may have included altered brain development, reduced birth weight, and diminished endocrine function through alterations in the hypothalamic-pituitary-adrenocortical axis [9]. A study was done in the Democratic Republic of the Congo; it focused on the effects on newborns of prenatal maternal stress on methylation of genes regulating the hypothalamic-pituitary-adrenocortical axis [7]. It was observed that chronic stress produced broad effects on the various components of the hypothalamic-pituitary-adrenocortical (HPA) axis. In this study, mothers, exposed to chronic stress and war trauma, had statistically significant methylation effects at transcription factor binding sites. This means that the stress-induced changes in the HPA axis led to specific epigenomic effects at important active genetic sites. The most important effects were in the following genes, corticotropin releasing hormone *(CRH)*, corticotropin releasing hormone binding protein *(CRHBP)*, nuclear receptor subfamily 3 group C member 1 *(NR3C1)*, and FK506 Binding Protein 5 *(FKBP5).* Each of these genes is linked intimately to the hypothalamic-pituitary-adrenocortical (HPA) axis and influences its functioning. This includes influencing infant birthweight. Another possible route of interaction between environmental exposures and changes in the epigenome may be through the serotonin transporter *(SERT)* gene. This gene has been implicated as a link between life stress and depression, although the precise molecular mechanisms modulating this link are not defined [11]. Epigenetic modification of SERT appears to play an important role in the etiology of depression in both pregnant mothers and young children. In a recent study of 133 healthy young adults [12] researchers in Germany observed that maternal prenatal stress and child maltreatment were both associated with a depressed SERT mRNA expression profile in an additive manner. In addition to the link between prenatal stress and depression, and the impact of prenatal stress on early postnatal car [6], there are additional findings. A potential association between prenatal insult stress and changes in gene expression has been demonstrated; this finding is implicated in developmental programming of various chronic diseases later in life [13].

Early life epigenetic effects

In the North American South in the decades before the Civil War, half of all enslaved African Americans were under the age of sixteen [9]. Young children were not exempt from torture. The mistreatment of children, both physically (through beatings and other forms of torture) and psychologically (through slave-owner initiated reward systems that encouraged them to betray their parents and other enslaved persons) is well documented in the literature. Early postnatal life is a critical period of brain development. Frequent exposures to malnutrition and childhood trauma affected health outcomes over the lifespan and into future generations. Within the last decade, researchers have published increasingly on the epigenetic mechanisms capable of explaining the impacts of new insults [14]. Sustained childhood trauma is associated with dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. Both HPA factors, *CRHBP* and *FKBP5*, increase the risk for suicidal behavior in children [15]. Indeed, suicides of enslaved African American children may have been masked in the historical literature as "accidents" according to the National Humanities Center [16]. Other researchers [17] suggests that actual suicide rates were low among enslaved African Americans and were consistent with suicide rates for continental Africans and African-ancestry peoples living in other parts of the world. Kneeland [17] proposed that low rates of suicide likely reflect cultural inhibitions to a practice that would have occurred only under the extreme conditions of oppression.

Late childhood and adolescence epigenetic effects

Adolescence is considered a critical developmental period when physical and cognitive abilities are optimized as frontal cortical functions mature to adult levels [18]. North American enslavement added two new profound conditions to which adolescents had to adapt. For boys and girls, the potential for being sold and permanently separated from family and friends much intensified, particularly for adolescent males. For teenage girls, the harsh reality of sexual exploitation, forced cohabitation, and pregnancy became much more likely. Adolescence is also the time that there was the full realization of the permanency of life-long bondage. Also, the enslaved adults in their lives, including their parents and mentors, could not protect them from punishment at the hands of their masters and other European-Americans. As the reality of their powerlessness became apparent, this realization must have been a source of profound psychological dismay. Along with this realization, we would expect to have seen alterations in the stress response as well as the beginnings of changes in physical health risk. This stress response would be expected to catalyze dysregulation associated with depression and other psychopathologies [19].

Maltreatment in late childhood and early adolescence has been studied and shown to produce characteristic changes in DNA methylation patterns [20]. Mehta's team, working in Germany, studied the impact of differences in sub-adult environments on adult disease-related genome-wide gene expression and DNA methylation patterns in peripheral blood cells. All of the study patients had Post Traumatic Stress Disorder (PTSD) and were divided into two groups. The first was an adult childhood-abuse group with PTSD; the second was a PTSD group without a history of childhood abuse. They subsequently observed significant distinct biological networks for the childhood-abuse group that suggested differences in the pathophysiology of PTSD. Maltreatment in this stage of the life cycle can become a salient independent factor influencing specific biological modifications ultimately producing a unique pathology of PTSD in adulthood [20]. Furthermore, the epigenetic effects observed in traumatized adolescents on the cusp of their reproductive lives may also be subject to intergenerational transmission, so that the epigenetic legacy of abuse could be expressed as well in the offspring of these adolescents. Epigenetically, these would be expressed in altered networks of neurotransmitters and neuromodulators including amines, amino acids, nitric oxide, and neuropeptides. An inflammatory response could be induced by the activation of these neuroimmune pathways [21].

Adult epigenetic effects

Depression disorders are the most common clinical outcome following trauma [22]. This was the case during slavery as it is today. Stress and childhood abuse were the most critical environmental triggers for adult-onset PTSD [23] among enslaved individuals as they would be today. Enhanced glucocorticoid receptor sensitivity is present in adults with PTSD, although the molecular mechanisms are still under investigation [24]**.** In a study of combat veterans, Yehuda and colleagues found that individuals with PTSD had lower levels of cytosine methylation in the promoter region in peripheral blood mononuclear cells (lymphocytes [T cells, B cells, NK cells] and monocytes), than did combat veterans without PTSD. This research concluded that the observed alterations might reflect enduring epigenetic modifications. If this is correct, then we would also expect that these epigenetic changes would be transmitted to future generations of Legacy African Americans.

An Overview of Associated Clinical Symptoms

At each **Table 1** depicts the clinical manifestations are likely to occur under the conditions of enslavement and/or exposure to institutionalized racism. Empty cells indicate areas where research on associated epigenetic changes remains lacking.

Epigenetic changes associated with significant trends in African American biological history provide a context for understanding the implications of this history on contemporary health disparities [83]. The picture we can paint from centuries of enslavement and exposure to debilitating racial discrimination however suggests that these environments produced long-term negative implications for enslaved African Americans and their descendants. However, the picture would also have to include significance evidence of resilience and adaptive survival mechanisms emerging that ameliorated many of the disadvantageous consequences of a sub-optimal environment [84]. The evidence for resilience mechanisms to partially

compensate for the adverse epigenomic consequences in response to the trauma of enslavement and institutionalized racism at various developmental stages is the topic of our future studies.

Table 1 Depicts the clinical manifestations that are likely to occur under the conditions of enslavement and/or exposure to institutionalized racism.

Clinical Effects Of Slavery/ Racism Trauma and Stress	Clinical References	Possible Associated Epigenetic Changes
Depressed mood/ sadness, mood swings	Van der Does [25] Hasler et al. [26] Perkovic et al. [27]	Alterations in expression of PCLO rs2522833 candidate polymorphisms [28] Histone acetylation, as well as DNA methylation/hydroxymethylation, in the mammalian CNS [29] Leukocyte mRNA levels in glucocorticoid receptor, neurotrophic factors, cell adhesion molecules, SR protein splicing factors, transcription factors, epigenetic factors (histone deacetylase, sirtuin, DNA methyltransferase) suggests use of state and trait markers in combination improves differential diagnoses [30] Alterations in brain derived neurotrophic factor (BDNF) controlled neuroplasticity [31] Lower methylation in glucocorticoid receptor regulator FK506 binding protein S [32]
Loss of interest or pleasure	Fried et al. [33] Winer et al. [85]	Environmental factors may contribute for neurodegeneration through induction of epigenetic modifications, such as DNA methylation, and chromatin remodeling, which may induce alterations in gene expression programs [34]
Trouble making decisions and remembering things	Kreutzer et al. [35] Karp [36]	
Significant weight changes (weight loss or weight gain)	Fried et al. [33] Knapen et al. [37]	Glucocorticoid sensitivity, abnormalities in plasma cortisol and HPA-axis function [38]
Changes in sleep (insomnia or sleeping too much)	Lovato and Gradisar [39] Taghva [40]	
Chronic fatigue	Garg et al. [41] Skapinakis et al. [42]	Biologic markers not yet identified [43] Hypomethylation within promoters of genes associated with immune cell regulation; multi-system dysregulation [44]
Feelings of hopelessness, guilt, and worthlessness	Zahn et al. [45] Newmann [46]	
Difficulty concentrating	Papakostas and Culpepper [47] Ohayon [48]	Damage to plasma phospholipids such as omega-3-fatty acid and docosahexonic acid [49]
Suicidal thoughts or attempts	Angst et al. [50] Lönnqvist [51] Masi et al. [52]	Hypermethylation of BDNF and TrkB, especially in Brodmann's Areas 8 and 9 [53]
Irritability	Vidal-Ribas et al. [54] Dalton et al. [55]	
Risk taking behavior	Leas and Mellor [56] Kosunen et al. [57] Hong et al. [58]	Differential methylation of CpG islands proximal to homeobox DLX1 gene [59]
Unexplained and persistent aches and pains	Jaracz et al. [60] Brannon et al. [61]	
Persistent sadness or anxiety	Stieglitz et al. [62] Horwitz and Wakefield [63] Rottenberg [64] Mathews et al. [65]	Histone deacetylation resulting in corticosteroid regulation of glucocorticoid receptor and subsequent corticotropin releasing factor expression in central amygdala [66]
General discontentment	Bracka et al. [67] Neckelmann et al. [68]	
Excessive crying	Haroz et al. [69] Kraemer and Hastrup [70]	
Social isolation	Holt-Lunstad et al. [71] Matthews et al. [72] Darling [73] Hakulinen et al. [75]	Alteration of the brain-derived neurotropic factor BDNF gene [74]
Self-blaming, hyper self-critical, pessimistic	Jansson and Nordgaard [76] Westerbeek et al. [77] Fisher et al. [78]	Methylation of the oxytocin receptor gene (OXTR) [79]
Fixation on past failures	Moore [80] Moulds et al. [81] Nolen-Hoeksema et al. [82]	

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