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Editorial

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The Biological Effects of Trauma

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The experience of psychosocial trauma or adversity is ever-pervasive in our society. A global population survey showed that 70% of respondents were exposed to traumas such as collective violence, interpersonal or intimate partner violence, and accidents/injuries [1]. This is alarming given that trauma or stress experienced during childhood and adulthood increases the risk for the development of psychopathology such as posttraumatic stress disorder and depression [2, 3], and physical ill health such as cardiovascular disease and diabetes [4–6]. Exposure to certain traumas appears to be sex-specific. For example, males are more likely to experience non-sexual assault and combat-related trauma, and females are more likely to be exposed to sexual assault and childhood sexual abuse. Overall, females report lower rates of trauma exposure but are twice as likely to be diagnosed with posttraumatic stress disorder than males [7], potentially indicating that trauma type, frequency, and timing may increase the risk for this disorder [8].

Exactly how an environmental exposure (such as trauma) "gets under our skin," that is, affects our biology in a long-lasting manner, remains unclear. One potential mechanism is via epigenetic modifications during critical periods in development which may lead to developmental programming of long-lasting adaptive and/or maladaptive responses to changes in the early life environment [9]. Epigenetics is the study of heritable changes in gene function that are not due to changes in the DNA sequence [10]. The most studied epigenetic changes in clinical settings, using peripheral (e.g., whole blood and saliva) and brain samples, are alterations in methylation at CpG dinucleotides. Early adversity has shown to increase or decrease the DNA methylation (DNAm) status of several CpG sites, mostly located in the regulatory regions (e.g., gene promoters) and in the genes *SLC6A4* (serotonin transporter), *NR3C1* (glucocorticoid receptor), *FKBP5* (regulates glucocorticoid receptor activity), and *IL6* (pro-inflammatory cytokine) [11, 12]. Many studies conducted in populations at risk for psychopathology show that the observed DNAm changes are in association with risk alleles; thus, suggesting that DNAm may mediate the observed gene-by-trauma interactions [13]. However, these candidate gene-by-environment interactions are not always replicated in the general population [14]. A more recent study showed that genetics and gene-by-childhood trauma interactions account for the majority of variance in DNAm compared to childhood trauma alone [15]. It is worth noting that genetic variation has

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also shown to influence risk for exposure to early adversity [16]. This is referred to as gene-environment correlation, defined as the genetic differences in exposure to certain environments [17, 18].

The pattern of epigenetic modifications generally correlates with the corresponding gene expression profile, where an overall negative correlation between promoter DNAm and gene expression has been canonically observed [19, 20]. As with DNAm, significant differences in gene expression levels have been observed in individuals who have experienced trauma compared to those who have not [21]. Furthermore, a distinct immune-related gene expression profile, known as common conserved transcriptional response to adversity, characterized by upregulation of the expression of genes involved in inflammation and downregulation of genes involved in type I interferon responses and antibody synthesis, has been observed in individuals exposed to chronic threat [22]. This type of immune transcriptional response has been seen in childhood trauma survivors, without any psychiatric diagnoses, after an acute psychosocial stressor [23]. The downstream effects of these immune-related gene expression changes in the peripheral and brain tissues, as a result of trauma, still need to be fully understood.

Interestingly, accumulating evidence suggests that the effects of trauma can be inherited intergenerationally. One of the first studies to observe this phenomenon was in the offspring of holocaust survivors who had a higher rate of psychopathology [24]. However, this offspring population also reported higher levels of childhood trauma [25] and resilience [26]. The intergenerational effects of trauma have also been studied in mothers who were pregnant during the Apartheid era in South Africa – the offspring of young mothers who had experienced greater stress had increased psychiatric morbidity than those whose mothers had experienced less traumatic stress during this time period [27]. Trauma is thought to be "transmitted" across generations through epigenetic mechanisms. For example, the offspring of Holocaust survivors had lower blood DNAm in *FKBP5,* especially in those whose mothers were exposed during childhood [28, 29], while their parents showed opposite effects (i.e., increased DNAm) at this gene [28]. Further, blood transcriptome analyses revealed glucocorticoid and immune-related gene alterations in association with parental Holocaust exposure [30]. Whole genome-wide DNAm analysis showed that individuals exposed to famine in utero had differential DNAm in regions related to development [31]. Another study showed that maternal exposure to childhood abuse was associated with sex-specific DNAm and expression alterations of the *BDNF* gene (encodes a neurotrophic factor) in the offspring [32]. Another multigenerational analysis of DNAm found limited evidence for intergenerational transmission [33]. These findings provide some evidence of the role that epigenetic influences may have in the intergenerational "transmission" of trauma; however, further research is needed to delineate and understand the exact mechanisms involved.

Studies on trauma, particularly trauma experienced during early life, are limited by methodological challenges. For example, many studies use retrospective self-report measures when assessing trauma, and this can be influenced by recall bias and an individual's subjective interpretation of an adverse event. Indeed, a systematic review found low concordance between prospective and retrospective measures of childhood maltreatment [34]. Furthermore, the method of data collection may also have an influence: face-to-face interviews may result in different trauma prevalence being recorded compared to telephone, self-administered, or computer-assisted surveys [35]. Finally, many of the published studies use peripheral measures of DNAm, which need to be expanded to large-scale molecular investigations of postmortem brains [36], and cell type-specific alterations [37].

It is clear that there is still much that we do not know about the effects of trauma on our biology, and much more investigation into this area is needed. Findings from research on the effects of trauma may inform the development of targeted intervention programs, with the ultimate goal of significantly decreasing the prevalence of trauma and its psychosocial and biological impact.

Conflict of Interest Statement

In the past 3 years, N.P.D. has held a part-time paid position at Cohen Veterans Bioscience, has been a consultant for Sunovion Pharmaceuticals, and is on the scientific advisory board for Sentio Solutions for unrelated work.

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S.D. and N.P.D. researched the topic, co-wrote the manuscript, and approved the final version of the manuscript.

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