Journal of Neuropsychology and Behavioral Processes

Volume 1 *Mentored Research* Article 4

2024

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Cover Page Footnote

Kevin P. Kaut (kpk@uakron.edu) is the corresponding author for this manuscript. The work was done entirely by Emma Griffith at the University of Akron as part of a senior honors thesis.

An epigenetically driven relationship between parental PTSD and inflammatory disease in offspring: A proposal

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Research and Education Aspiring to Cultivate Humanity (REACH)

Journal of Neuropsychology and Behavioral Processes:

Human Behavior

Volume 1

Inaugural Edition:

Mentored Research

Abstract

Could a combat veteran's horrific experiences in early-2000s Afghanistan have a direct, biological impact on his or her now-adult daughter's risk of a heart attack later in her life? This concept would have been unapologetically mocked a mere twenty years ago, and it has only been in the past decade that the new field of epigenetics has revealed a distinct possibility for this event to actually take place—for parents' experiences to profoundly influence the biology of their children. The major objective of this research project is to argue for the legitimacy of this theoretical phenomenon by discussing the latest data regarding PTSD's interaction with the epigenome, the various epigenetic markers associated with PTSD, the numerous health detriments that have been observed in conjunction with these specific biomarkers, and the reported heritability of these epigenomic alterations. In conclusion, this manuscript will establish the foundation for this hypothetical event to be cogently argued for while simultaneously calling for more real, concrete studies to be conducted on the subject matter to evaluate its biological validity and potential effect on human health.

Current statistics suggest psychological trauma is an established phenomenon of the human condition, with approximately 80-90% of the population reporting a personal experience with one or more *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (Criterion A) traumatic event(s), such as a natural disaster, warzone combat, or sudden death of a family member [2, 30, 71]. However, the clinical diagnosis of posttraumatic stress disorder (PTSD)—a response to trauma that includes persistent flashbacks to the traumatic event, marked avoidance of sensory associations to the traumatic event, extreme hypervigilance, negative emotional states, etc. (Figure 1)—occurs at a much lower rate within the population; lifetime prevalence estimates of PTSD fall around 7% [30]. The central discussion in PTSD research revolves around its cause and effect; why does this small portion go on to develop the disorder, and how does this long-term posttraumatic stress biopsychosocially affect the individual?

While previous research into PTSD, under various colloquialisms such as “shell shock” and “war neurosis,” has principally revolved around psychological characteristics, recent technological and scientific advancements have allowed modern traumatic stress research to extend into the biological sciences, specifically genetics and

Probiscus Publications est. 2023

Emma N. Griffith completed this work as part of her Honors research. K.P.K. was her academic advisor and is the corresponding author for this work.

immunology [139, 173, 184]. The studies conducted at this intersection of biology and psychology with respect to PTSD have contributed significantly to our understanding of traumatic stress alongside more successful medication options, therapeutic strategies, and prophylactic measures, encouraging researchers to further untangle this complex disorder by potentially substituting a psychological emphasis for a physiological one.

Arguably, dysregulated immune response has become the most noteworthy biological relationship with PTSD, with inflammatory disease occurring much more frequently in PTSD cases than in the general population [45]. Many studies are identifying much higher levels of inflammatory biomarkers such as C-reactive protein (CRP) and tumor necrosis factor (TNF) alongside a significantly higher prevalence of inflammatory diseases such as cardiac issues, autoimmune disorders, and metabolic diseases in those living with PTSD [104; 142]. While the exact cause of this PTSD-inflammation relationship is under investigation, many are pointing to a dysregulation of the hypothalamic-pituitary-adrenal axis (HPA-axis) that connects the stress response to the immune system [138]. Even more interestingly, there is mounting evidence that this abnormal immune response correlates with epigenetic changes within the individual [117].

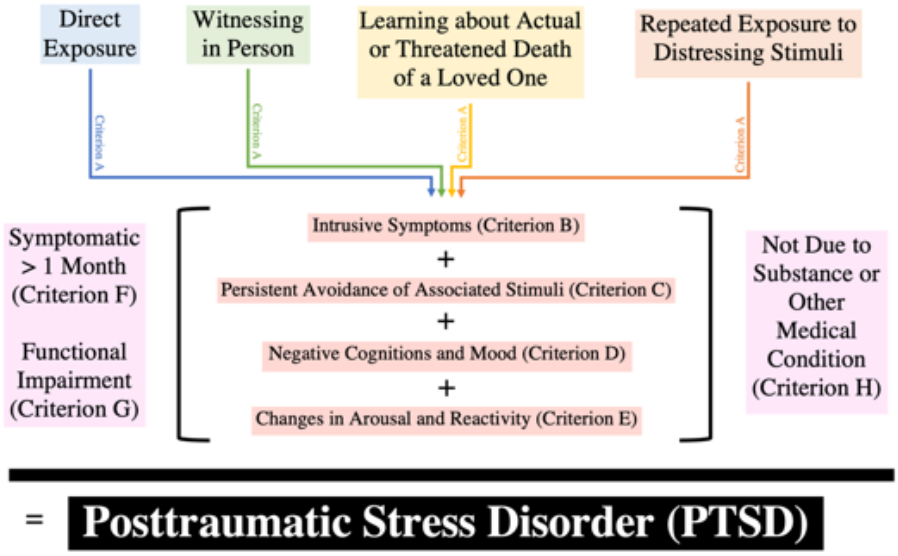

Figure 1. Illustration of Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for diagnosis of Posttraumatic Stress Disorder. Criterion A characteristics are shown at the top of the figure (e.g., Direct Exposure; Witnessing in Person) and converge on Criterion B (Intrusive Symptoms).

The scientific term "epigenetic" refers to that which is outside of the genome itself, or the immediate biochemical environment surrounding the genome that does not affect the sequence of the genome but rather influences genetic expression [39]. When discussing epigenetics, there are two main epigenetic modifications that can occur: histone modifications and—the event at the center of this review—DNA methylation (DNAm) [53]. In short, DNAm occurs when a methyl (CH_3) group is added to a DNA molecule, usually to the fifth carbon atom of a cytosine ring [53] (see Figure 2). In the vast majority of cases, this addition of a methyl group silences the gene by obstructing the binding of transcriptional factors to DNA, effectively turning the gene off [53]. However, the opposite can also occur, where a previously methylated gene can become unmethylated or hypomethylated, effectively turning the gene on [53]. DNAm levels, while relatively stable throughout cell replication, are notorious for responding sensitively to certain environmental stimuli, such as smoking, exposure to toxins, radiation, and diet changes, resulting in a gene's methylation status, and therefore genetic expression, to change [154]. These biological environmental stimuli (smoking, diet, etc.) easily translate into physiological repercussions, but increasing evidence is supporting the notion of psychological stimuli also translating into physiological consequences [154]. More specifically, psychological stress is also making its way onto the list of environmental stimuli that occur in step with specific patterns of DNAm change, especially

Epigenetic:
A reference to that which is outside of the genome itself – not affecting the genetic sequence of nucleotides, but the expression of genetic information.

in genes relating to the immune system and ensuing health disparities [4, 16, 52, 57, 81, 89, 99, 140, 173].

PTSD's involvement with the epigenome then naturally brings into question various concerns of heritability and whether DNAm patterns could be transmitted to subsequent human generations. This occurrence, known as epigenetic inheritance (EI) has served as a contentious topic ever since the introduction of epigenetics in the 1940s, with traditional genetics rejecting EI in mammals (humans) while some leave the door open for possibility [40]. EI has been well-documented and supported in plants and insects, observed in fish species, and documented sparsely in mammals [7, 11, 22, 61, 64, 67, 100, 129, 147]. However, this low documentation rate could easily be explained by the presupposition of most researchers that EI simply does not occur in mammals, leading to its lack of study and subsequent support, which then erroneously confirms the presumption of its nonexistence. Additionally, the environmental confounds that come from studying EI in mammals (gestational period, nursing, etc.) can make studying this phenomenon exceptionally difficult [148]. Although, many evolutionary arguments exist for EI occurring in mammals as it does in other organisms, and studies that have been successful in limiting the confounding variables have found documented cases of EI primarily in mice [34, 185]. In humans, many heritable diseases —including most inflammatory diseases—suffer from a "missing heritability," where only a portion of the heritability is assigned to genetics [167]. This raises an important question guiding the work reported here: could EI contribute to these gaps in human health disparities? Moreover, and specific to the context of this paper, could a parent's experience with a stress related circumstance such as PTSD contribute to a child's inflammation-related health issues via DNAm?

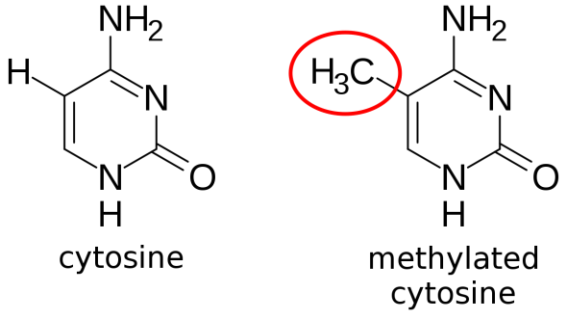

Figure 2. Methylation (addition of CH3) of a cytosine ring. Cytosine is one of the nucleic acids comprising the 'vocabulary' of DNA (adenine, cytosine, guanine, thymine).

From: *https://en.wikipedia.org/wiki/DNA_methylation*

In short, many studies have recently implicated a significant relationship between a PTSD diagnosis, body-wide inflammation, and an epigenetic occurrence known as DNA methylation that could possibly be inherited. Therefore, the aim of this paper is to evaluate the current literature addressing the theoretical validity of a heritable dysregulated immune response originating in parental posttraumatic stress disorder.

The Relationship between PTSD, DNA Methylation, & Inflammation

As stated previously, the past twenty years of psychobiological research into PTSD has yielded a correlation between a clinical diagnosis, epigenetic changes, and a dysregulated immune response [99]. The focus of this section is to connect these three variables through the results of diverse studies thus separating the relationship into its three sub-relationships: PTSD and inflammation, PTSD and DNA methylation changes, and DNA methylation changes and inflammation. Once this foundation is established for an epigenetic contribution to PTSD's immune involvement, the second half of this paper will address the possible heritability of these repercussions.

PTSD & Inflammation/Immune Dysregulation

The idea of a causal relationship between posttraumatic stress and an inflammatory response appears to be the newest evolution in the study of the stress response. Beginning in 1936, Hans Selye provided experimental evidence of the immune system and gut changing mechanistically in response to overstimulation of the adrenals—the primary glands involved

in releasing stress-related hormones [159]. Four decades later, Fischer et al. [41] investigated this phenomenon with major surgery acting as the stimulus for the adrenal overarousal, reporting the many ramifications that come with extensive surgical trauma, including endocrine and immune system involvement. Di Padova et al. [33] further specified this involvement as dramatic acute increases in interleukin-1 (IL-1) inhibitors (i.e., hinders leukocyte functioning; [82]), interleukin-6 (IL-6; encourages inflammation at injury site [160]), and C-reactive protein (CRP; indicator of inflammation presence [171]) in middle-aged women who underwent major surgery. Three decades later, these results remain supported as Sadahiro et al. [143] found comparable results among a small cohort of elderly individuals showing significant increases in IL-6 and CRP from baseline to immediately after surgery and to hospital discharge. Over the course of these findings, many studies pointed to the stress-induced activation of the hypothalamic-pituitary-adrenal axis (HPA) as a potential origin of this inflammatory response [54, 106, 186], as the HPA has direct influence on both the immune and stress responses [32, 58]. Naturally, this pointed to the HPA as a mediator between stress and the immune system, leading to many research projects on whether the stress involved in activating the HPA could be generalized beyond physiological trauma [70, 94, 162, 166]. In other words, could psychological trauma also instigate this inflammatory response? If this does occur, what impact would a perpetual state of stress, and therefore inflammation, have on an individual's health?

Interleukins: Proteins produced and released by white blood cells (leukocytes), which influence activity in the immune system.

The past twenty years have yielded numerous studies addressing these questions with consistent and significant results. Miller et al. [105] examined a cohort of 286 US military veterans and compared CRP levels in PTSD cases (~57%) versus non-PTSD cases (~43%). As expected, those with PTSD were significantly more likely to have clinically elevated levels of CRP [105]. Plantinga et al. [132] found similar results when using a sample of twin pairs where one had a clinical diagnosis of PTSD and the other did not, reporting the largest association between high-sensitivity (higher threshold for significance) CRP (hsCRP) and PTSD. The twin with PTSD had an average hsCRP level 30% higher and an average intercellular adhesion molecule 1 [ICAM-1; crucial in inflammatory process [114]] level 9% higher than their non-PTSD counterpart after adjusting for potential confounds [132]. A sample of 130 Japanese women (57 with a PTSD diagnosis and 73 controls) revealed a significantly higher IL-6 levels among PTSD cases [123]. Among a sample of 60 refugees, the 25 men and women with PTSD had significantly higher levels of IL-1β (facilitates leukocyte functioning; [82]), IL-6, and TNF- α (pro-inflammatory protein involved in the immune response [24]) than controls [47]. The most popular and significant biomarkers within these studies appear to be CRP, IL-6, and TNF—all of which are pro-inflammatory and play key roles in the immune response—but other biometrics are also usually explored as well. Most samples within this area of study come from populations with regular trauma exposure, such as combat veterans, sexually abused women, individuals with low socioeconomic status (SES), etc.

Could psychological trauma also instigate an inflammatory response? If this does occur, what impact would a perpetual state of stress, and therefore inflammation, have on an individual's health?

Appendix 1 offers a summary of recent studies comparing inflammatory biomarkers in PTSD/trauma cases versus controls. As can be seen from Appendix 1, CRP, IL-6, and TNF are becoming an established biological covariate among those with posttraumatic stress disorder, while other biomarkers (IL-18, IL-1β, ICAM-1) are less studied and require more data. An important caveat must be noted in analyzing these studies as a whole and inferring generalization: publishing negative or non-significant results is an extremely difficult task [108], so the prevalence of such significant results may indeed be unrepresentative and must be examined with caution. However, non-significant results were not uncommon in this review; in Appendix 1, these inflammatory biomarkers were nonsignificant in 25 out of 53 tests—nearly half. Additionally, the observation that significant findings were nearly uniform under CRP, IL-6, and TNF and most of the non-significance occurred under less-studied

biomarkers indicates then that this positive publication bias is not of great concern. Overall, the current biometric data within PTSD cases suggest inflammation as playing a prevalent role within the stress disorder.

The relationship between PTSD and elevated inflammation also appears to be more nuanced than a simple dichotomy; rather, this phenomenon has been documented as a continuous, scaled correlation [158]. For example, Bertone-Johnson et al., [6] found that an official PTSD diagnosis was not necessary in order for an increase in inflammation: a sample of sexually abused women with no screening for PTSD revealed higher inflammatory levels than controls. More specifically, CRP and IL-6 were 20-50% higher in women who reported sexual abuse compared to those reporting no sexual abuse [6]. Similarly, Carvalho et al. [18] observed a negative bidirectional relationship between CRP levels and SES, and Carroll et al., [17] also observed significantly higher IL-6 levels among adults who reported having low SES during the first two years of their life. However, these studies simply designated life stress/trauma exposure or a PTSD diagnosis as the variable of interest; only a select few delineated between trauma/no PTSD and PTSD cases [45, 158]. For example, Sumner et al. [158] did distinguish between trauma and PTSD cases among middle-aged women in their methodology, and they found the relationship between traumatic stress severity and TNF level to be continuous and linear [158]. In other words, women with no trauma had the lowest TNF levels, women with trauma but no PTSD diagnosis had significantly higher TNF levels than those with no trauma, and women with PTSD had significantly higher TNF levels than the women with trauma but no PTSD diagnosis [158]. Even within a PTSD diagnosis, more traumatic exposure appears to correlate to more immune activation [173]. Furthermore, research is beginning to recognize that individuals who had PTSD but are now recovered have decreased inflammatory levels than their current-PTSD counterparts [133], or even have levels similar to the general population [63]. As a whole, the research into this relationship between psychological stress and an immune response indicates a positive correlation between the two; an increase in the severity of the traumatic stress leads to a proportional increase in levels of inflammatory biomarkers. For a visualization of this relationship, refer to Figure 3.

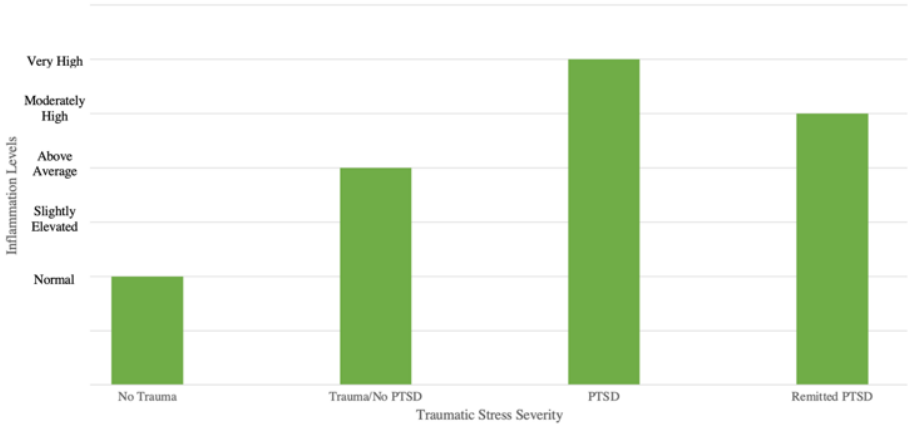

Figure 3. Inflammation levels as a function of traumatic stress severity.

From these data, the next natural question considers whether these increased inflammatory levels have any clinical significance: is there a significant detriment on the health of these individuals that can be traced back to this psychoneuroimmunological relationship? If this effect did exist among this population, then there would be an expectation for an abnormally high rate of inflammatory/immune disease, such as cardiac issues, autoimmune diseases, certain metabolic deficiencies, etc. [101]. Indeed, many studies have reported a significantly increased risk for cardiac events/cardiac-related mortality among those with PTSD [8, 142]. Specifically, those with PTSD have been found to be nearly twice as likely to have hypercholesterolemia, insulin resistance, angina, heart attack, and emphysema [168]. Immunologically, rheumatoid arthritis, an autoimmune disease specifically attacking joint synovium [91], was significantly more prevalent in individuals who had experienced childhood trauma [156]. Furthermore, O'Donovan et al. [126] found the rate of diagnosis for specific autoimmune diseases, such as thyroiditis, inflammatory bowel disease, multiple

sclerosis, rheumatoid arthritis, and systemic lupus erythematosus, was significantly higher among Iraq and Afghanistan veterans.

Altogether, the immunological component to PTSD/trauma appears to reach not only a statistical significance, but also a clinical one, where this increase in inflammation can be inferred as the culprit for these seemingly unrelated health detriments in those with PTSD. As stated previously, this translation of traumatic stress into immune response is likely mediated by the HPA axis [54, 106, 186]. However, the questions remain, how and why this bodily mechanism operates in such fashion. Many recent studies have probed into this inquiry, and the finding of epigenetic modifications—namely, DNA methylation—to certain HPA-related and immune system genes proves to be a consistent one [99]. The following subsection will accumulate the current data on this association between PTSD and the differential methylation status of certain inflammatory genes.

PTSD & DNA Methylation

Referring back to the earlier definition, "epigenetics" refers to the genome's immediate surrounding biochemical environment that determines the expression of corresponding genes [39]. An organism's epigenetic makeup and genetic expression smoothly adapts according to its ecology, suggesting that environmental factors can induce epigenetic modifications that allow the organism to better adapt to its circumstances [92]. There are two primary biological mechanisms through which these epigenetic changes take place: histone modifications and DNA methylation (DNAm) alterations [53]. DNAm has a much larger body of literature behind it in this regard [191] and will therefore be the focus of this topic's epigenetic component. While the complexity of DNAm is beyond the scope of this paper, a fundamental description (see Figure 2) simply involves the adding or removing of a methyl (CH_3) group typically to the fifth carbon atom of a cytosine ring in a DNA molecule [53]. In gene sites that are unmethylated, transcriptional factors bind to the DNA molecule and then the corresponding gene segment is transcribed for later translation (i.e, protein production), thus allowing for the gene's instruction to be expressed within the organism to an extent corresponding to the prevalence of methylation [109]. However, when a gene is totally methylated, this methyl group (CH_3) prevents the transcriptional factors from binding to the DNA molecule and therefore prevents the gene's expression [109]. It is also worth noting that the methylation status of a gene is not dichotomous in the sense of whether it is unmethylated or methylated; rather, variation in levels of methylation exist due to many different loci within single genes [109]. In summary, a gene's hypermethylation (i.e., increased methylation status) usually corresponds to its silencing, and a gene's hypomethylation (i.e., reduced status) corresponds to its expression. The context of psychological PTSD/trauma presents an intriguing context to this epigenetic circumstance; the environmental stimuli traditionally considered in this research setting included variables with direct biological relevance, like diet, exposure to toxins or radiation, medication intake,

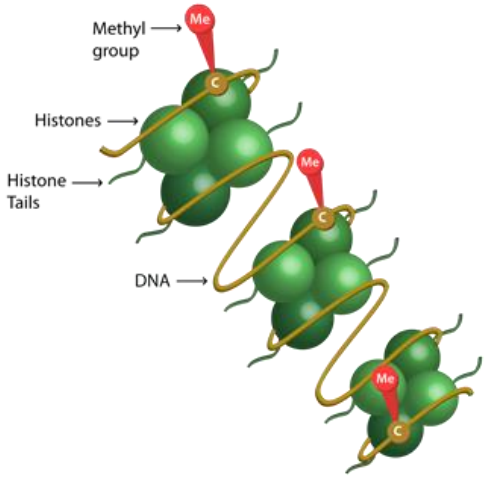

Figure 4. Methylation of cytosine (C) bases on a strand of DNA (gene). A single strand of DNA is shown coiling around histone bodies. NOTE: on a single strand of DNA, the four bases include Adenine, Cytosine, Guanine, Thymine. The sequence of these bases comprises a gene itself. Sufficient methylation (Me) can interfere with the enzyme *DNA transcriptase*, thus preventing the transcription (i.e. copying) of the DNA base sequence into messenger RNA (mRNA) for later translation (i.e., protein production). Image available at https://www.epigentek.com/catalog/dna-methylation-c-75_21.html

etc. [154]. Thus, the addition of psychological stimuli to this list of possible pathways to epigenetic modification was not considered until nearly a decade ago when researchers began to discover this link between the immune system and psychological hardship [17]. This psychoneuroimmunological interaction then invoked the epigenome when researchers began consistently noting the differential methylation status of various immune-related genes in PTSD cases.

This connection between posttraumatic stress and the immune system initially appears unrelated but becomes entirely sensical when taken in the context of the HPA and its far-reaching network with a number of biological systems. This being said, the exact mechanism behind which this process occurs is less clear, but many recent studies are pointing to epigenetic modifications as a possible avenue, especially considering the prevalent and consistent observation of immune system genes among PTSD cases. For example, Uddin et al. [173] noted that genes related to immune system functions were significantly overrepresented among uniquely unmethylated genes in PTSD cases. Additionally, Hammamieh et al. [52] conducted a DNAm study including combat veterans with and without PTSD, and approximately 60% of the differentially methylated genes between the two sets of veterans predominantly functioned in the immune system. However, the question of causality remains: is a pre-trauma state of heightened inflammation to blame for PTSD's development post-trauma, or is trauma the invoker of immune system response? In both scenarios, DNAm stands as a possible common point of origin between the two. To untangle this issue, Rusiecki et al. [141] took a cohort of military service members and measured pre- and post-deployment methylation levels of two genes involved in genetic instability and the innate immune system (LINE-1 and Alu). One of the genes, LINE-1, was found to be significantly hypomethylated in PTSD cases versus the trauma-exposed controls [141]. The following year, Rusiecki et al. [140] took a similar cohort of US military members and also measured their pre- and post-deployment DNAm levels of IL-18, a gene that encodes for a protein that attracts immune cells to sites of injury or infection [68]. The IL-18 gene of members who came back meeting the diagnostic criteria for PTSD was, in fact, significantly hypomethylated [140]. In both of the Rusiecki et al., studies [140, 141], the data implicates this hypomethylation as a response to deployment (i.e., trauma exposure) and that a previous inflammatory state is not necessarily to blame for PTSD development. Rather, traumatic stress appears as a stimulus of epigenetic changes that induce (or at least contribute to) inflammation and immune dysregulation.

Before discussing the specific genes of interest, the methodological burdens of studying epigenetics first need to be addressed in order to properly appreciate the results. The number of documented genes within the human genome is constantly increasing, and most of them have multiple functions that are also regularly being updated [144]. Therefore, studies on this topic typically require a candidate gene method, where researchers presume an effect based on current scientific consensus and focus on only a few specific genes per study [112]. In other words, scientific technology is currently unable to conveniently test every gene in the entire human genome for methylation status; therefore, geneticists are obligated to pursue gene hypotheses that stem from previous lines of study rather than inefficiently test an unwieldy number of genes. Additionally, negative results are extremely difficult to publish, as previously explained [108], and the number of significant/positive results in this domain most likely pale in comparison to the countless non-significant/negative results. Combining this dominant candidate gene methodology and a lack of published non-significance, most studies in this realm will present significant results relating to specific genes. Therefore, the weight of the PTSD-DNAm studies summarized here is not dependent on frequency of significance, but rather on frequency of replication.

While methylation's general impact on gene expression was described earlier, its effect in the context of specific genes also needs to be elucidated before presenting the most-studied candidate genes. Referring back to the earlier discussion on the basic mechanisms of DNAm, hyper-methylation typically corresponds with a gene's silencing, and hypo-/demethylation corresponds with a gene's expression [53]. The effect of this silencing/expression is, therefore, subsequently dependent on the gene's original function within the immune system. For example, FKBP5 codes for an immunoregulatory protein, so

its observed *hyper*methylation in Holocaust survivors [190] would indicate the silencing of this gene, the lack of its regulatory element, and ultimately an extent of immune dysregulation. Similarly, the IL-12 gene codes for its protein that activates T-cells [80], and its observed *hypo*methylation in PTSD cases [4] would presumably result in an over-expression of this gene and a high level of its pro-inflammatory protein. That being said, Appendices A & B summarize the most common genes studied on the relationship between methylation and PTSD/trauma.

The linear relationship between inflammation and trauma discussed in the previous subsection also appears to apply when DNAm is additionally considered; the methylation in these immune system genes seems to also wax/wane in accordance with the amount of traumatic exposure and the function of the gene. With an adult cohort of Detroit residents, Bustamante et al. [14] compared DNAm levels of NR3C1, a gene involved in the HPA-immune response, among individuals exposed and not exposed to maltreatment during childhood. They found a significant hypermethylation of NR3C1 among the childhood maltreatment group, with no delineation between PTSD cases and non-PTSD cases [14]. Furthermore, Smith et al. [150] focused on the DNAm of AHRR, a gene whose methylation could promote immune dysregulation through decreased levels of kynurenine [an immune system activator [72]]. This study utilized a trauma-exposed sample, comparing those with PTSD to those without PTSD, and found that their hypothesis was supported: PTSD cases had significantly higher levels of DNAm of AHRR than the trauma-exposed controls [150]. In other words, Bustamante et al. [14] found a significant difference in methylation between the trauma-exposed and the not trauma-exposed, and Smith et al. [150] found a significant difference in methylation between trauma-exposed/no PTSD and PTSD cases—suggesting a critical relationship between traumatic stress severity, DNAm of immune-related genes, and inflammation.

DNA Methylation & Inflammation/Immune Dysregulation

In addition to the separate correlations between a) PTSD and inflammation, and b) immune system genes' DNAm level and PTSD, a third sub-relationship between c) DNAm and inflammation is also worth briefly expounding upon. The majority of cases included in this review either report hypermethylation of immunoregulatory genes, thus decreasing the expression of the gene and decreasing immunoregulation, or report hypomethylation of pro-inflammatory genes, thus increasing the gene expression and overall strength of the immune response (see Appendices A & B). Overall, this lack/abundance of DNAm promotes immune system dysregulation and appears as a contributing factor to PTSD's perpetual inflammatory state. Furthermore, studies implicate this change in DNAm as a hindrance to bodily regulation and a catalyst for health issues such as cardiovascular disease, atherosclerosis, hypertension, and general inflammation [193]—similar consequences previously stated when discussing the correlation between PTSD and inflammatory disease. While Appendices A & B present a mixture of hypo- and hypermethylation findings, inflammatory disease in the absence of traumatic exposure has been correlated with the slight trend of hypomethylation across the genome [48], reinforcing this separate relationship between DNAm and inflammation. Additionally, certain autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Grave's disease (GD), and systemic sclerosis (SSc)—common comorbidities among those with PTSD [156; 126]—present similar methylation patterns that implicate immune system dysregulation [20]. Moreover, abnormal methylation patterns have been suggested as a potential contributor to cancer development [180], another detriment prevalent among those with PTSD [137]. Overall, the connection between abnormal immune-related gene methylation and inflammatory disease presents intriguing insight into the connection between PTSD, DNAm, and the immune system. However, as alluded to earlier, the causal direction of these relationships between trauma/PTSD, methylation changes, and immune dysregulation remains obscure; traumatic stress appears to be the instigator, however, questions remain: does the resulting DNAm/inflammation give way to PTSD symptoms? Or, does PTSD manifest epigenetically and therefore *contribute to* the chronic inflammation? Alternatively, is this an unfortunate cycle of inflammation causing PTSD which then causes more inflammation?

Relational Direction between PTSD, DNA Methylation, & Inflammation

When discussing the possible causal directions of this relationship, a general consensus does not necessarily exist. Most studies acknowledge extreme/traumatic stress as the originator of immune system methylation changes [105, 149, 173], but the mysterious relationship between the resulting inflammation and PTSD is highly speculative. For example, Speer et al. [155] implies inflammation as a driver of PTSD symptoms. Similarly, Mehta et al. [99] noted that immune system genes were dysregulated in PTSD cases *prior* to trauma exposure in a few studies, suggesting that the *a priori* inflammatory state facilitated the development of PTSD after the traumatic event. However, Michopoulos et al. [101] argues that the perpetual activation of the HPA that comes with PTSD—and not PTSD in and of itself—is the originator of this chronic inflammation. Studies on this specific question are rare, and a longitudinal methodology is needed for proper inference and such studies are difficult to logistically employ in this research context. Regardless of the exact sequence of events, which requires considerably more data and innovative research methods before it can be clarified, the relationship between PTSD, DNAm, and chronic inflammation is well documented (Appendices A & B). Nevertheless, the science is certainly not anywhere near settled here, and there is much work to be done in the future to go beyond relationships among variables toward a more definitive sense of causal direction. Indeed, factors influencing clarity in this area of research include the well-known emphasis on publishing statistically significant findings and the nature and sophistication of available research methodology.

Non-Significant Results & Insufficient Research Methods

Published negative results are uncommon [108], as previously noted, but this does not mean they are absent from the literature entirely. In terms of measuring inflammatory biomarkers within PTSD/trauma, a few studies did not report significance when comparing levels of inflammatory biomarkers (CRP, IL-6, TNF, IL-18, IL-8, IL-2, IL-4, and IL-10) between PTSD/trauma and controls [5, 50, 124]. Additionally, this review has focused on human studies, meaning that data collection was limited to non-invasive mediums (saliva, bloodwork, etc.) that may not be entirely representative of an individual's true biological composition. Lastly, most studies reviewed in this paper (refer to Appendices A & B) on the relationship between PTSD and inflammation took a sample from a very narrow population (e.g., Iraqi refugees [153], middle-aged African American women with diabetes [133], etc.), so the generalizability of findings may be compromised. These limitations do not nullify the significant results found, however, considering significance has been found across methodological differences and disparate populations. When studying DNAm, an entirely different set of challenges must be addressed. Firstly, the vast majority of studies presented here employ a cross-sectional design, which does not logically allow for causal inferences [112]. Longitudinal designs are needed, but the logistics of such a method are onerous, especially when involving genetic research [112]. Additionally, candidate-gene methods (the majority of studies presented here) are notoriously difficult to replicate [77]. As previously discussed, the rarity of published non-significant results and the common employment of candidate-gene methods forces the scientific currency to shift from significant versus non-significant results to straight replication frequency. For example, in Appendix B, the most frequently replicated gene (FKBP5) was replicated four times. Nevertheless, the inclusion of DNAm in this relationship between PTSD and inflammation is gaining considerable support despite these limitations.

This invoking of the (epi)genome via DNAm then organically invokes the novel possibility of the genetic line and whether these immune system issues could potentially be passed down through generations, all originating in parental PTSD/trauma. The following section discusses the theoretical validity and practical feasibility of this prospect.

Epigenetic Inheritance

The concept of epigenetic inheritance—the passing down of the epigenome (i.e., histone modifications and the DNA methylome)—naturally arises when discussing these changes associated with PTSD and inflammation since they are closely associated with the actual genomic sequence. In the context of this manuscript, this possibility more specifically reduces to whether a parent's experience with severe trauma or PTSD could alter his/her epigenome via the DNAm of (mainly) immune system genes, result in inflammation issues, and even pass this pro-inflammatory state on his/her children through epigenetic inheritance (EI), potentially resulting in the child's increased risk for inflammatory disease. However, EI in mammals (e.g., humans) is extremely controversial, with traditional biology denying its hypothetical existence for reasons that will be discussed later. The aim of this section is not necessarily to argue for EI in humans, but rather to argue for open mindedness towards the possibility and push for mammalian EI to be revisited in the context of recent research exhibiting epigenetic changes associated with psychopathologies. This section will begin by explaining EI terminology, followed by climbing up the plant-animal kingdom with respect to documented EI, presenting current evolutionary arguments for and against EI in mammals/humans, discussing the many obstacles researchers face in studying this phenomenon. We conclude by calling for human EI to be reconsidered within biology in this modern context where stress-related disorders (PTSD, etc.) are increasingly understood to have epigenetic effects contributing to disease load.

Epigenetic Inheritance Terminology

Like any other subject, the field of epigenetics carries a unique vocabulary. As explained earlier, "epigenetic inheritance" (EI) refers to passing down of the genome's immediate biochemical environment alongside the genetic information, primarily in the form of histone modifications and DNA methylation levels [39, 53]. When this inheritance is discussed in terms of generations, researchers will commonly use the delineation of "F0" (F-zero) as the original generation, "F1" as the first offspring, "F2" as the offspring's offspring, and so forth. Additionally, some researchers will use "intergenerational" and "transgenerational" interchangeably when considering EI, but for our purposes, their differentiation is necessary. Intergenerational EI (IEI) refers to inheritance in the timespan of direct exposure to the organism at some point in development [113]. For example, IEI occurs in males when a stimulus is presented to F0, modifies F0's epigenome and haploid chromosomal material in spermatazoa, and F1 inherits this modification; F1 was, in a way, directly exposed to the

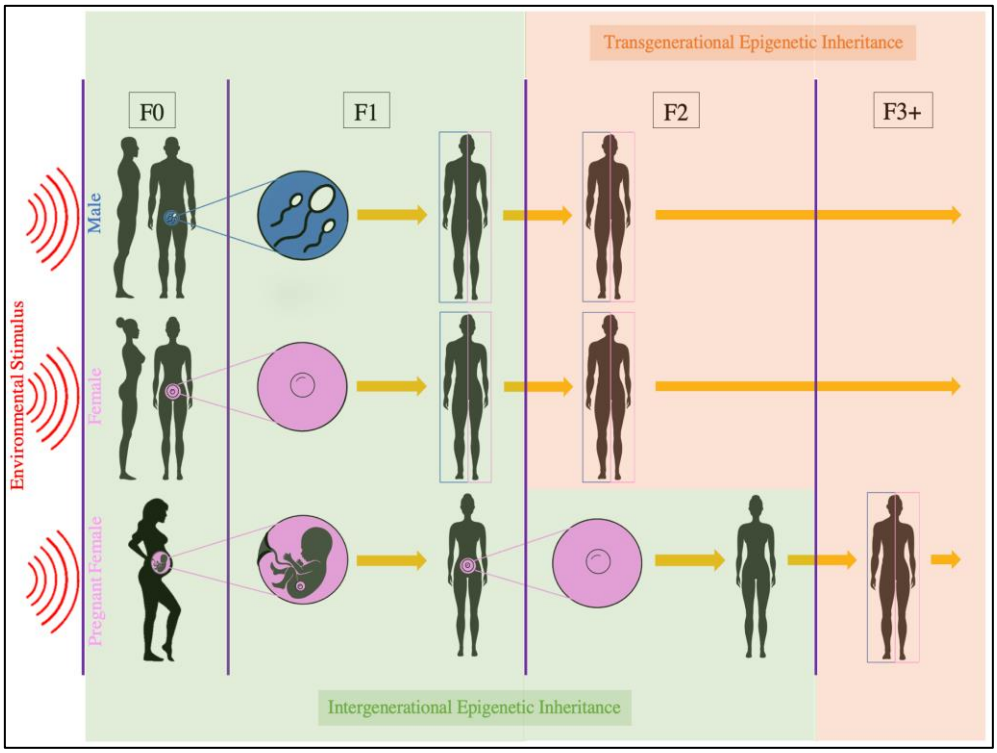

Figure 5. Intergenerational transmission of epigenetic modification.

stimulus through the paternal germline [113]. For females, the extent of IEI is entirely dependent on the organism's reproductive process and the female's reproductive status (pregnant vs. not pregnant). In the context of this paper and its focus on human EI, female IEI in humans can extend to the F2 generation due to the gestational period [113]. If F0 was presented a stimulus while pregnant with female offspring (F1), then F1's eggs (F2) were technically directly exposed to the stimulus as a primordial germ cell (PGC) in the F1 female fetus developing in the womb of F0 [113]. In other words, intergenerational EI occurs when offspring are directly exposed to the environmental stimulus as (primordial) germ cells or a growing fetus and subsequently modifies the offsprings' epigenome in a similar manner to F0 [113]. Transgenerational EI (TEI), however, occurs when this inheritance continues on with no direct stimulus exposure; for males, this would be the F2 generation and beyond, for females, the F3 generation and beyond [113]. Mammalian/Human TEI is documented very rarely and is much more controversial in the field of genetics for reasons that will be subsequently discussed. In summary, the difference between IEI and TEI reduces to direct exposure (see Figure 5 for an illustration of this difference). The definitions and terminology described in this section are germane to this discussion and will be frequently used throughout the remainder of this manuscript.

Documented Epigenetic Inheritance in the Plant-Animal Kingdom

Since the focus of PTSD's potential epigenetic effect in previous sections focused on DNAm, the EI discussed here will also be limited to DNAm. Generally speaking, EI occurs frequently among organisms lower on the evolutionary scale and gradually becomes less frequent as organisms become higher ordered [22]. DNAm EI appears to be best documented in plant species, with many researchers reporting stable TEI of the methylome in weeds (*Arabidopsis thaliana*) [61, 107], flowering plants. (*Linaria vulgaris*) [28], tomato species [84], oil palms [121], corn [38], and many others [61, 164]. With insects, stable DNAm EI has been documented in flies (TEI, *Drosophila*) [188], wasps (EI, *Nasonia*) [183], aphids (TEI, *Acyrthosiphon psium*) [157], honeybees (IEI, *Apis mellifera*) [189], beetles (IEI, *Leptinotrsa decemlineata*) [12], and others [165]. Researchers have observed similar DNAm inheritance in fish, specifically recorded in inland silverside fish (TEI, *Menida beryllina*) [83], half-smooth tongue sole fish (TEI, *Cynoglossus semilaevis*) [21], and zebrafish (IEI, *Danio rerio*) [67]. Only one study was found investigating EI in reptiles (specifically, painted turtles, *Chrysemys picta*), and the results were non-significant [42]. Mammalian EI—especially TEI—is naturally intriguing due to its human applications, and so there is a decent repository of literature [22], especially in mice [9, 27, 111, 136]. Studies of note include Wei et al. [185] reporting IEI via DNAm in pre-diabetic mice and Dias & Ressler [34] documenting TEI of smell responses due to fear conditioning in mice. In fact, this TEI observed in Dias & Ressler [34] was traced back to significantly decreased DNAm at the relevant odorant receptor gene. However, many biologists and geneticists deny its authentic occurrence because of traditional biological consensus, its evolutionary drawbacks, and the methodological flaws inherent to these studies.

The Controversy surrounding Mammalian Epigenetic Inheritance

With the prevalence of documented EI in plants, insects, fish, and even mice, why does modern biology outright reject its possible extrapolation to all mammals and even humans? Why is this original prospect of paternal PTSD contributing to offspring inflammatory disease met with automatic dismissal? The established observation of epigenetic erasure—the resetting of the epigenome in mammalian development [122]—primarily answers this inquiry, in addition to the seeming lack of evolutionary benefit and common issues in current research designs. Within mammalian—and therefore, human—development, DNAm patterns are completely reset (demethylated) at the moment of conception and during the production of cells that will eventually become the individual's gametes [primordial germ cells (PGCs)] [122]. In other words, mammalian embryos start with little to no epigenetic baggage; even if the DNA methylation patterns within a female's egg or a male's sperm are altered due to

environmental stimuli experienced throughout the lifespan, the moment of fertilization would largely erase both unique patterns of methylation from the mother and father. Therefore, mammalian EI is considered abnormal and a result of a failure of the "typical" erasure process [7, 22, 78, 88]. Additionally, the documented cases of mammalian EI rarely offer any long-term benefits; McCarthy et al. [93] reported TEI in mice but documented the phenotype to be detrimental rather than adaptive. Furthermore, erasure ensures that the embryonic cells are able to differentiate into specialized cells (totipotency) [25]. Wang et al. [181] even postulates that this epigenetic erasure may be critical to placental development during gestation. The overall evolutionary argument against mammalian EI is lacking, but its effect is widely seen as maladaptive while the opposing epigenetic reset is widely seen as developmentally necessary for one reason or another [64]. Consequently, mammalian IEI is characterized is rare and mammalian TEI as baseless within the biological realm [64]. The compounding rarity of mammalian EI appears to add to this evolutionary argument [64]: if it has no benefit and is even detrimental, it would not be regularly occurring or else the entire species would devolve. Finally, the difficulty in producing studies that would allow for a direct causal inference and a ruling out of environmental confounders and unforeseen variables is nearly impossible with mammals and their gestational period, and this escalates into further problems when studying incredibly complex, socially interwoven, highly intelligent human beings. Based on these assertions, researchers have thoroughly rendered mammalian/human EI out of biological bounds and not worth attempting to research. However, the founding premise of this argument upon which the evolutionary and methodological objections stand (the epigenetic erasure process) is rising again into the literature in light of new scientific and technological advancements. In other words, the totality of mammalian epigenetic erasure is slowly becoming less solid in research, alongside more evolutionary arguments *for* mammalian EI and the deconstruction of methodological excuses for this theoretical phenomenon to go on uninvestigated.

It has long been known that a small subset of ~100 genes—intracisternal A particle (IAP) genes—are resistant to this methylation erasure, or "imprinted" [102, 148]. IAPs remain almost wholly protected through both phases of epigenetic reprogramming and could very possibly act as a vessel for mammal/human EI [102]. Although, studies are beginning to discover more sites that are resistant to this erasure beyond IAPs. For example, Seisenberger et al. [145] reported IAPs' general protection from reprogramming in mice (a common model for human research) but also found 233 other sites that did not undergo reprogramming. Furthermore, Tang et al. [161] explored these sites in mice that resist erasure and found epigenetic marks specifically associated with multiple sclerosis (MS), obesity, and schizophrenia. While no studies on non-IAP, erasure-resistant genes have been conducted with human samples, many researchers are considering the number of human IAPs to be much greater than ~100 [29]. Moreover, Szyf [152] documents more than 40% of all methylation sites retaining their methylation patterns in adult PCGs. Overall, these studies give an interesting precedent for researchers to investigate, especially when the potential health detriments of inflammatory epigenetics associated with PTSD/trauma is implicated.

There are also a number of evolutionary arguments for regular mammalian/human EI postulated in recent literature. As previously explained, the initially adaptive EI observed in mice from McCarthy et al. [93] progressed into maladaptive phenotypes that negatively affected the generational lines. At face value, this argues against mammalian EI, but Prokopuk et al. [134] explains how (epi)genetic mutations prioritize immediate survival over potential long-term issues. This then circles back to the initial topic of this paper: PTSD, inflammation, the HPA, etc. Theoretically, what would be the evolutionary benefit of increased inflammation in response to extreme stress or trauma? Clearly, our modern existence is far removed from our natural roots, but Miller & Raison [103] argue that the inflammatory response during psychological stress is ingrained from our evolutionary beginnings when instances of severe stress almost exclusively occurred alongside the body's inflammatory response to injury (predator attacks, sickness, etc.). Over time, this association presumably manifested

biologically, hence this present-day physiological relationship between psychological trauma and inflammation [103]. Even in our twenty-first century lives, this association between inflammation and PTSD/trauma remains via survival threats; for example, the horrific injuries sustained by combat veterans undoubtedly invoked a massive inflammatory response that occurred alongside a psychological trauma. In the context of PTSD, this inflammation-associated trauma is chronically re-experienced through flashbacks, nightmares, and other PTSD symptoms, likely resulting in this chronic immune dysregulation. Additionally, many rheumatologists and immunologists consider chronic stress as an instigator of immune diseases [49], and immune diseases in turn increase the risk of psychopathology [66]. However, what survival reasons exist for this phenomenon to be passed down to offspring? Extrapolating this idea, the inheritance of this response would potentially be prophylactic and preparatory to offspring if they were to experience the same survival threats as their ancestors, even with the negative long-term effects of this pro-inflammatory state. Admittedly, this is conjecture and not documented evidence, but mammalian EI would additionally help explain the heritable adaptations that develop much faster than typical natural selection [167]. Furthermore, Sharma [147] argues, "epidemiological data supports existence of germline epigenetic inheritance also in humans," implying that recent data on the origins of human diseases very much allows for the occurrence of human EI. Overall, this evolutionary reasoning for the EI of PTSD-instigated chronic inflammation is far from irrational or outlandish.

Methodologically, several problems do exist in contemporary research with confounding variables, logistical difficulties, etc. [55, 64, 110, 118, 134, 148], but most of the opposition and lack of literature on this potential phenomenon comes from a presupposition that it does not regularly occur and is therefore not worth exploring. In light of this discussion of an expanding literature on erasure-resistant genes and evolutionary explanations, the premise of biological rarity or irregularity is moot. Furthermore, if EI has a significant impact on human health, as hypothesized here with PTSD and inflammation, the issue of research becomes soberly more pressing.

Any evidence of human epigenetic inheritance via DNA methylation?

In spite of these methodological troubles that come from studying human DNAm EI, a small number of researchers have reported significant results that decrease in frequency as the EI progresses towards transgenerational. Usually, EI is in the context of an environmental stimulus being presented to a pregnant mother and the methylation changes also being detected in the child (technically termed "fetal programming") [22]. For example, Hilakivi-Clarke & de Assis [60] argue that a mother's diet while pregnant with a female fetus can significantly affect the child's risk for breast cancer during adulthood. Intergenerationally, Dr. Marcus Pembrey presented work at the Latsis Symposium in 2017 that detailed a peculiar relationship between maternal grandmother smoking during pregnancy and granddaughters' higher risk for autism that is suspected to be mediated by DNAm changes [10]. Pembrey et al. [129) also found that a father's childhood smoking was correlated with increased body mass index (BMI) in sons, but not daughters. Transgenerationally, Pembrey et al. [130] also found an association between paternal grandfathers' childhood food supply and mortality risk in grandsons, and between paternal grandmothers' childhood food supply and mortality risk in granddaughters. Altogether, these few documented instances of EI in humans should exhort more researchers to investigate this possibility as well. However, only three studies were found observing results that are relevant to the specific phenomenon proposed in this paper—trauma, DNAm changes, inflammation, and potential epigenetic inheritance of immune system dysregulation.

EI as it relates to PTSD has been explored by three recent studies: Mehta et al. [100], Perroud et al [131], and Cao-Lei et al. [16]. Mehta et al. [100] gathered a cohort of veterans (with and without PTSD) and tested for a correlation between the veterans' DNAm levels at sixty-nine erasure-resistant candidate genes in their sperm to the mental health history of

their now adult children. Ninety percent of these candidate genes had significantly different DNAm levels in veterans associated with adult child mental illness [100]. Specifically, two genes were significantly associated with veteran (paternal) PTSD and adult child mental health condition(s): FKBP5 and NR3C1 [100]. Looking back to Appendix B, these two genes were among the most studied and best replicated among immune system related genes that were differentially methylated in PTSD. The old adage of "correlation does not equal causation" rings especially true in this study, but the significant association should be given its due credence. Similarly, Perroud et al. [131] examined Rwandan women who were pregnant during the Tutsi genocide of 1995. They compared Rwandan women who lived through this horrific time and Rwandan women who were not living in Rwanda when they were pregnant, and measured DNAm levels of candidate genes in these women and the children of their pregnancy. Perroud et al. [131], too, found significantly higher levels of DNAm of NR3C1 among mothers with PTSD and their children. Cao-Lei et al. [16] approached similarly, where they gathered women who were pregnant during (or were soon pregnant after) the Quebec ice storm of 1998, and measured their objective and subjective "maternal hardship," and then measured the DNAm levels in the children of their pregnancy. Cao-Lei et al. [16] found that prenatal maternal objective hardship was significantly correlated with DNAm levels in 1,675 methylation sites in the children, with 957 (~57%) of these sites primarily involved in immune system functioning. Interestingly, they report that the children's LTA gene (an immunoregulatory gene, also presented in Appendix B) had the most (18) differentially methylated sites that correlated with objective maternal hardship [16]. Again, these studies present correlations in situations where causality would be extremely difficult to infer, but they set a notable precedent for experts to conduct innovative research where such causality could be practically examined. Together, the relationship between PTSD, inflammation, and DNAm changes is considerably well-documented, but the realistic possibility of passing on this PTSD-associated immune dysregulation to descendants is severely lacking in data presumably due to an outdated, common consensus of mammalian EI rarity that has been thoroughly challenged in this section.

IV. Conclusions & Calls for Research

Finally, it should be noted that should this phenomenon prove supported in future research, it would very likely extend to other stress-related and anxiety disorders such as reactive attachment disorder, adjustment disorder, generalized anxiety disorder, obsessive-compulsive disorder, etc., considering the intimate relationship shared between the immune system and chronic stress/anxiety via the HPA. While PTSD was the center of this paper, it should serve only as a representative and not as a stand-alone disorder. PTSD occurs in about 7% of the population [30], but lifetime prevalence of all stress-related and anxiety disorders ranges from <1% [62] to 30% [128]. Similarly, up to 45% of Americans suffer from at least one chronic disease [135], and most immunologic conditions are innately tied to chronic stress and psychopathology [49, 66]. In fact, a large portion, ~50% [187], of heritability in these conditions is usually unaccounted for and generally unexplained [85], and many researchers are now considering epigenetic modifications as a possible explanation [167, 194]. Could it be that our modern, stressful lives are not only hurting us, but also our progeny?

As a whole, the aim of this review was to present a data-driven, scientific argument for researchers to investigate the potential for epigenetic inheritance of the pro-inflammatory state associated with PTSD. In other words, this review sought to build a case for the realistic questioning of whether a parent's experience with PTSD could theoretically lead to the child's diagnosis of autoimmune disease, eventual cardiovascular disease, etc. The first half of this paper comprehensively details the complex relationship documented between PTSD/trauma, body-wide inflammation, and corresponding DNAm changes, presenting the most common inflammatory biomarkers associated with PTSD (CRP, IL-6, TNF, etc.; Appendix A) and the most differentially methylated immune system genes in PTSD/trauma (FKBP5, NR3C1, etc.;

Appendix B). The entire first half of this review implicated PTSD/trauma as the first event in the sequence that induced DNAm changes and a chronic inflammatory state that has been associated with many chronic diseases like autoimmune diseases, cardiovascular issues, cancer, etc. This invoking of the epigenome and its contribution to serious health detriments naturally led to the second half of this paper: an address of the current evidence on whether this PTSD-associated immune dysregulation could be transmitted through the generational line despite an offspring's lack of exposure to direct psychological trauma. The data on epigenetic inheritance occurring in lower-level organisms (plants, insects) up through mammals/humans was shown, alongside a discussion of why mammalian/human EI data is significantly lacking, the evolutionary arguments for and against human EI, and an explanation of the few studies who specifically researched EI in the context of PTSD. As a whole, this review offers an extensive appraisal of the current literature regarding PTSD/trauma, inflammatory response, DNAm, and EI, and argues for this phenomenon to be creatively researched in light of the many health detriments associated with chronic inflammation alongside the potential for doctors and families to take action in preventing heritable inflammatory disease should it originate in parental PTSD.

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Appendix A

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Biomarker and Hypothesis	Relevant Findings	Population	Comparisons	Authors
C-Reactive Protein (CRP): protein secreted by the liver during an immune response; pro-inflammatory [17] Hypothesis: increases with trauma/PTSD	higher concentrations are significantly related to health-related quality of life significant positive association with PTSD	women	assaultive trauma history and PTSD *vs.* assaultive trauma history and no PTSD *vs.* no assaultive trauma history or PTSD	Gill et al., 2012 [45]
	positive association of hsCRP with past and current PTSD	monozygotic and dizygotic twin pairs born between 1946 and 1956 (during Vietnam War era)	≥ 1 twin was diagnosed with either PTSD and/or depression *vs.* both twins free from PTSD and depression	Plantinga et al., 2013 [132]
	women with PTSD had significantly higher average levels of CRP over a 10-16 year period	middle-aged women	trauma exposure and PTSD, *vs.* trauma exposure and no PTSD, *vs.* no trauma exposure and no PTSD	Sumner et al., 2017 [158]
	significant associations between hsCRP and five distinct PTSD symptoms: disengagement, depersonalization, derealization, memory disturbance, and identity dissociation hsCRP levels significantly higher in women with current and remitted PTSD compared to controls	middle-aged African-American women with diabetes and high rates of trauma exposure	current PTSD *vs.* remitted PTSD *vs.* no PTSD *vs.* depression *vs.* no depression	Powers et al., 2019 [133]
	probable PTSD was significantly associated with higher CRP levels	women with history of experiencing interpersonal violence	probable PTSD *vs.* no probable PTSD *vs.* probable depression *vs.* no probable depression	Heath et al., 2013 [56]
	CRP levels were 20-50% higher in women who reported sexual abuse compared to those not reporting sexual abuse	women	history of sexual abuse *vs.* no history of sexual abuse	Bertone-Johnson et al., 2012 [6]
	CRP levels significantly positively associated with PTSD, traumatic events, and deprivation CRP levels significantly negatively associated with social support and SES	individuals of European descent	PTSD *vs.* no PTSD	Carvalho et al., 2019 [18]
	significant difference in levels of hsCRP between groups of veterans with PTSD, remitted PTSD, and no PTSD	veterans	current PTSD *vs.* remitted PTSD *vs.* no PTSD	O'Donovan et al., 2016 [125]
	lower CRP levels among PTSD cases	Swiss patients	involved in accident requiring surgery with no PTSD *vs.* PTSD patients	von Känel et al., 2007 [179]
	lower CRP levels among Iraqi refugees	Iraqi refugees	PTSD *vs.* no PTSD	Söndergaard et al., 2004 [153]
	no significant correlation between CRP and PTSD	general	PTSD *vs.* no PTSD	Baumert et al., 2013 [5]

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Biomarker and Hypothesis	Relevant Findings	Population	Comparisons	Authors
Interleukin-6 (IL-6): cytokine produced at the location of inflammation during an immune response; pro-inflammatory [160] Hypothesis: increases with trauma/PTSD	higher concentrations of IL-6 were significantly related to health related quality of life	women	assaultive trauma history and PTSD *vs.* assaultive trauma history and no PTSD *vs.* no assaultive trauma history or PTSD	Gill et al., 2012 [45]
	soluble IL-6 levels higher in current PTSD than remitted PTSD	physically healthy women with history of divorce/separation	current PTSD *vs.* remitted PTSD *vs.* no PTSD	Newton et al., 2014 [119]
	IL-6 levels higher in women who reported sexual abuse compared to those not reporting sexual abuse	women	history of sexual abuse *vs.* no history of sexual abuse	Bertone-Johnson et al., 2012 [6]
	IL-6 levels significantly higher levels in PTSD patients	general	severely affected PTSD patients *vs.* healthy controls	Gola et al., 2013 [47]
	IL-6 levels significantly higher in PTSD cases	general	veterans with PTSD *vs.* healthy controls	Hammad et al., 2012 [51]
	early life SES significantly negatively associated with IL-6 levels	Caucasian individuals	SES *vs.* biomarkers (correlation analysis)	Carroll et al., 2011 [17]
	NS	monozygotic and dizygotic twin pairs born between 1946 and 1956 (during Vietnam War era)	≥ 1 twin was diagnosed with either PTSD and/or depression *vs.* both twins free from PTSD and depression	Plantinga et al., 2013 [132]
	NS	Swiss patients	involved in accident requiring surgery with no PTSD *vs.* PTSD patients	von Känel et al., 2007 [179]
	NS	earthquake-exposed individuals	PTSD *vs.* no PTSD	Wang et al., 2019 [182]
	NS	combat-exposed males	PTSD *vs.* no PTSD	Lindqvist et al., 2014 [79]
Tumor Necrosis Factor (TNF): protein produced by white blood cells during immune response; key protein in acute inflammatory response; pro-inflammatory [24] Hypothesis: increases with trauma/PTSD	higher average levels of TNF-II among women with PTSD over a 10-16 year period women with trauma but no PTSD had significantly higher levels than those without trauma and lower levels than those with trauma and PTSD	middle-aged women	trauma exposure and PTSD, *vs.* trauma exposure and no PTSD, *vs.* no trauma exposure and no PTSD	Sumner et al., 2017 [158]
	TNF-alpha levels significantly higher in PTSD patients	general	severely affected PTSD patients *vs.* healthy controls	Gola et al., 2013 [47]
	soluble TFNR2 levels significantly higher in women with past history of sexual abuse	women	history of sexual abuse *vs.* no history of sexual abuse	Bertone-Johnson et al., 2012 [6]
	TFN levels significantly higher levels in PTSD cases	combat-exposed males	PTSD *vs.* no PTSD	Lindqvist et al., 2014 [79]
	TFN levels significantly higher levels in PTSD cases	earthquake-exposed individuals	PTSD *vs.* no PTSD	Wang et al., 2019 [182]
	NS	Swiss patients	involved in accident requiring surgery with no PTSD *vs.* PTSD patients	von Känel et al., 2007 [179]

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Biomarker and Hypothesis	Relevant Findings	Population	Comparisons	Authors
Interleukin-18 (IL-18) or Interferon Gamma Inducing Factor IFN-γ: cytokine primarily produced by macrophages; modulates immune responses; pro-inflammatory [35] Hypothesis: increases with trauma/PTSD	IL-18 levels significantly higher levels in PTSD cases	combat-exposed males	PTSD *vs.* no PTSD	Lindqvist et al., 2014 [79]
	IFN-gamma and IFN-alpha significantly higher in PTSD cases	general	veterans with PTSD *vs.* healthy controls	Hammad et al., 2012 [51]
	NS	general	PTSD *vs.* no PTSD	Baumert et al., 2013 [5]
	gene expression of IL-18 decreased in PTSD cases	general	PTSD *vs.* controls	Zieker et al., 2007 [195]
	NS	Iraqi and Syrian refugees	screened probable PTSD *vs.* no PTSD	Grasser et al., 2020 [50]
	NS	earthquake-exposed individuals	PTSD *vs.* no PTSD	Wang et al., 2019 [182]
Interleukin-1β (IL-1β): protein created by macrophages that facilitates leukocyte function during infection/immune response; pro-inflammatory [82] Hypothesis: increases with trauma/PTSD	IL-1β levels significantly higher in PTSD patients	general	severely affected PTSD patients *vs.* healthy controls	Gola et al., 2013 [47]
	IL-1β levels significantly higher in PTSD cases	earthquake-exposed individuals	PTSD *vs.* no PTSD	Wang et al., 2019 [182]
	NS	combat-exposed males	PTSD *vs.* no PTSD	Lindqvist et al., 2014 [79]
	NS	Swiss patients	involved in accident requiring surgery with no PTSD *vs.* PTSD patients	von Känel et al., 2007 [179]
Interleukin-10 (IL-10): cytokine produced from varioustypes of immune-related cells that works to limit host immune response; anti-inflammatory [65] Hypothesis: complex; initial increase and then decrease	NS	Swiss patients	involved in accident requiring surgery with no PTSD *vs.* PTSD patients	von Känel et al., 2007 [179]
	IL-10 levels significantly higher in PTSD cases	general	veterans with PTSD *vs.* healthy controls	Hammad et al., 2012 [51]
	NS	earthquake-exposed individuals	PTSD *vs.* no PTSD	Wang et al., 2019 [182]
Intercellular Adhesion Molecule 1 (ICAM-1): crucial molecule in immune mediation and inflammation; pro-inflammatory [114] Hypothesis: increases with trauma/PTSD	ICAM-1 levels significantly higher levels in twins with PTSD	monozygotic and dizygotic twin pairs born between 1946 and 1956 (during Vietnam War era)	≥ 1 twin was diagnosed with either PTSD and/or depression *vs.* both twins free from PTSD and depression	Plantinga et al., 2013 [132]
	higher average ICAM-1 levels among women with PTSD over a 10-16 year period	middle-aged women	trauma exposure and PTSD, *vs.* trauma exposure and no PTSD, *vs.* no trauma exposure and no PTSD	Sumner et al., 2017 [158]
Interleukin-4 (IL-4): key cytokine secreted to regulate antibody production and inflammation; anti-inflammatory [43] Hypothesis: decreases with trauma/PTSD	IL-4 levels significantly lower in PTSD patients	Swiss patients	involved in accident requiring surgery with no PTSD *vs.* PTSD patients	von Känel et al., 2007 [179]
	NS	earthquake-exposed individuals	PTSD *vs.* no PTSD	Wang et al., 2019 [182]

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Biomarker and Hypothesis	Relevant Findings	Population	Comparisons	Authors
Vascular Cell Adhesion Molecule 1 (VCAM-1): protein produced to moderate the adhesion of lymphocytes, monocytes and other immune-related cells to the inner lining of blood vessels; pro-inflammatory [73] Hypothesis: increases with trauma/PTSD	NS	monozygotic and dizygotic twin pairs born between 1946 and 1956 (during Vietnam War era)	≥ 1 twin was diagnosed with either PTSD and/or depression *vs.* both twins free from PTSD and depression	Plantinga et al., 2013 [132]
	NS	middle-aged women	trauma exposure and PTSD, *vs.* trauma exposure and no PTSD, *vs.* no trauma exposure and no PTSD	Sumner et al., 2017 [158]
Interleukin-2 (IL-2): protein secreted to mediate interactions among leukocytes; pro-inflammatory [120] Hypothesis: increases with trauma/PTSD	NS	earthquake-exposed individuals	PTSD *vs.* no PTSD	Wang et al., 2019 [182]
	NS	general	PTSD patients *vs.* healthy controls	O'Donovan et al., 2016 [125]
White Blood Cell (WBC): cells within the bloodstream that fight against infection (leukocytes); indicative of inflammation [59] Hypothesis: increases with trauma/PTSD	NS	monozygotic and dizygotic twin pairs born between 1946 and 1956 (during Vietnam War era)	≥ 1 twin was diagnosed with either PTSD and/or depression *vs.* both twins free from PTSD and depression	Plantinga et al., 2013 [132]
Interleukin-1 (IL-1): regulatory cytokine of inflammation and innate immune response; pro-inflammatory [69] Hypothesis: increases with trauma/PTSD	IL-1 predicting PTSD severity; negative trend	Iraqi and Syrian refugees	screened probable PTSD *vs.* no PTSD	Grasser et al., 2020 [50]
Fibrinogen: clotting factor secreted from the liver in response to injury; pro-inflammatory [3] Hypothesis: increases with trauma/PTSD	NS	monozygotic and dizygotic twin pairs born between 1946 and 1956 (during Vietnam War era)	≥ 1 twin was diagnosed with either PTSD and/or depression *vs.* both twins free from PTSD and depression	Plantinga et al., 2013 [132]
Interleukin-8 (IL-8): cytokine produced in response to inflammation; mediator of the immune response; anti-inflammatory [31] Hypothesis: increases with trauma/PTSD	NS	earthquake-exposed individuals	PTSD *vs.* no PTSD	Wang et al., 2019 [182]
Interleukin-13 (IL-13): regulatory cytokine of the immune response; associated with inflammation; anti-inflammatory [87] Hypothesis: increases with trauma/PTSD	NS	earthquake-exposed individuals	PTSD *vs.* no PTSD	Wang et al., 2019 [182]

Appendix B

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Gene ↓ Encoded Protein ↓ Protein's Immune System Purpose	Relevant Findings	Population	Comparisons	Authors
K506 (Tacromlimus) Binding Protein (FKBP5) ↓ FKBP5 ↓ immunoregulatory protein; modulates glucocorticoid receptor activity during stress response [192]	significant interaction between SES and site type on FKBP5 low childhood SES was associated with increased DNA at shore/shelf sites	general older adults	SES *vs.* DNAm (correlation study)	Needham et al., 2015 [117]
	neighborhood social environemnt was associated with FKBP5 DNAm	general US adults aged 55-95	SES *vs.* DNAm (correlation study)	Smith et al., 2017 [151]
	significantly higher FKBP5 DNAm levels in Holocaust survivors	general	Holocaust survivors and their adult offspring *vs.* demographically similar parents and children	Yehuda et al., 2016 [190]
	NS	general	9/11 World Trade Center responders *vs.* controls	Kuan et al., 2017 [74]
Nuclear Receptor Subfamily 3 Group C Member 1 (NR3C1) ↓ Glucocorticoid Receptor (GR) ↓ manages genes involving various bodily functions, including the inflammatory response [177]	women exposed to genocide had significantly higher methylation levels of NR3C1	pregnant Rwandan women	widows exposed to the Tutsi genocide *vs.* women living abroad	Perroud et al., 2014 [131]
	significant and consistent association between exposure to childhood maltreatment and hypermethylation of NR3C1	general	exposure to childhood maltreatment *vs.* controls	Cecil et al., 2020 [19]
	NS	general	9/11 World Trade Center responders *vs.* controls	Kuan et al., 2017 [74]
Brain Derived Neurotrophic Factor (BDNF) ↓ BDNF ↓ recruits peripheral immune cells to the brain [46]	significant interaction between childhood SES and site type on DNAm in BDNF	general older adults	SES *vs.* DNAm (correlation study)	Needham et al., 2015 [117]
	neighborhood social ennvironment was significantly associated with BDNF DNAm	general US adults aged 55-95	SES *vs.* DNAm (correlation study)	Smith et al., 2017 [151]
	NS	general	9/11 World Trade Center responders *vs.* controls	Kuan et al., 2017 [74]
Killer Cell Lectin Like Receptor G1 (KLRG1) ↓ KLRG1 ↓ inhibits natural killer cells and T cell function [175]	uniquely unmethylated in PTSD-affected individuals	individuals in Detroit	PTSD-affected *vs.* PTSD-unaffected	Uddin et al., 2010 [173]
	significant interaction between childhood SES and site type on DNAm in KLRG1	general older adults	SES *vs.* DNAm (correlation study)	Needham et al., 2015 [117]
	significant association between neighborhood socioeconomic disadvantage and methylation of KLRG1	general US adults aged 55-95	SES *vs.* DNAm (correlation study)	Smith et al., 2017 [151]

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Gene ↓ Encoded Protein ↓ Protein's Immune System Purpose	Relevant Findings	Population	Comparisons	Authors
Interleukin-8 (IL-8) ↓ IL-8 ↓ recruits immune cells to the infection site [68]	uniquely unmethylated in PTSD-affected individuals	individuals in Detroit	PTSD-affected *vs.* PTSD-unaffected	Uddin et al., 2010 [173]
	IL-8 receptor upregulated in PTSD	general	PTSD patients *vs.* controls	Zieker et al., 2007 [195]
	significant changes in methylation levels from pre- to post-deployment	US military service members	pre-deployment *vs.* post-deployment	Rusiecki et al., 2013 [140]
Antiviral Protein (AVP) ↓ Prepro-AVP (Vasopressin) ↓ can downregulate innate immunity during antigen exposure [90]	significant interaction between childhood SES and site type on DNAm in AVP AVP DNAm was significantly associated with SES	general older adults	SES *vs.* DNAm (correlation study)	Needham et al., 2015 [117]
	neighborhood social environment was significantly associated with AVP DNAm	general US adults aged 55-95	SES *vs.* DNAm (correlation study)	Smith et al., 2017 [151]
IL-18 ↓ IL-18 ↓ influences interferon-γ (INFG) production from T cells and natural killer cells [115]	IL-18 was differentially expressed in PTSD patients	general	PTSD patients *vs.* controls	Zieker et al., 2007 [195]
	IL-18 receptor was differentially regulated in PTSD	African Americans with low SES and high rates of trauma and PTSD	PTSD *vs.* no PTSD	Mehta et al., 2011 [98]
Solute Carrier Family 6 Member 4 (Serotonin Transporter) (SLC6A4) ↓ SLC64A ↓ strongly affects and modulates immune cells, among other bodily functions [146]	neighborhood socioeconomic disadvantage was significantly associated with SLC6A4 DNAm	general US adults aged 55-95	SES *vs.* DNAm (correlation study)	Smith et al., 2017 [151]
	NS	general	9/11 World Trade Center responders *vs.* controls	Kuan et al., 2017 [74]
Chemokine (C-C Motif) Ligand 1 (CCL1) ↓ CCL1 ↓ regulates and attracts T cells [75]	neighborhood social environment associated with CCL1 DNAm	general US adults aged 55-95	SES *vs.* DNAm (correlation study)	Smith et al., 2017 [151]
	significant interaction between childhood SES and site type on DNAm in CCL1	general older adults	SES *vs.* DNAm (correlation study)	Needham et al., 2015 [117]

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Gene ↓ Encoded Protein ↓ Protein's Immune System Purpose	Relevant Findings	Population	Comparisons	Authors
Cluster of Differentiation 1-d (CD1d) ↓ CD1d ↓ activates natural killer T cells [127]	significant interaction between childhood SES and site type on DNAm in CD1D	general older adults	SES *vs.* DNAm (correlation study)	Needham et al., 2015 [117]
	neighborhood social environment was significantly associated with CD1D DNAm	general US adults aged 55-95	SES *vs.* DNAm (correlation study)	Smith et al., 2017 [151]
Factor VIII (F8) ↓ F8 ↓ crucial for blood clot formation [169]	significant interaction between childhood SES and site type on DNAm in F8	general older adults	SES *vs.* DNAm (correlation study)	Needham et al., 2015 [117]
	neighborhood social environment was significantly associated with F8 DNAm	general US adults aged 55-95	SES *vs.* DNAm (correlation study)	Smith et al., 2017 [151]
NLR Family Pyrin Domain Containing 12 (NLRP12) ↓ Monarch-1 ↓ strongly mitigates inflammation [170]	significant interaction between childhood SES and site type on DNAm in NLRP12	general older adults	SES *vs.* DNAm (correlation study)	Needham et al., 2015 [117]
	neighborhood social environment was significantly associated with F8 DNAm	general US adults aged 55-95	SES *vs.* DNAm (correlation study)	Smith et al., 2017 [151]
Interleukin-12 (IL-12) ↓ IL-12 ↓ activates and regulates T cells [80]	increased expression of IL-12 in PTSD alongside relevant epigenetic markers significant hypomethylation of IL-12β in PTSD promoter of IL-12β was significantly hypomethylated in PTSD	general	veterans with from the Persian Gulf, Iraq, and Afghanistan Wars *vs.* age-matched controls	Bam et al., 2015 [4]
Toll Like Receptor 1 (TLR1) ↓ TLR1 ↓ assists in preventing tissue damage related to the immune response [23]	TLR1 uniquely unmethylated in PTSD-affected individuals	individuals in Detroit	PTSD-affected *vs.* PTSD-unaffected	Uddin et al., 2010 [173]
Toll Like Receptor 3 (TLR3) ↓ TLR3 ↓ vitally recognizes pathogens and initiates the adaptive immunity process [176]	TLR3 uniquely unmethylated in PTSD-affected individuals	individuals in Detroit	PTSD-affected *vs.* PTSD-unaffected	Uddin et al., 2010 [173]
	significant interaction between childhood SES and site type on DNAm in TLR3	general US adults aged 55-94	SES *vs.* DNAm (correlation study)	Needham et al., 2015 [117]