Review Article

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Genetic Alterations in War-Related Post-Traumatic Stress Disorder: A Systematic Review

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ABSTRACT

Objectives: This systematic review explored gene expression and DNA methylation patterns to identify key pathways and molecular targets associated with post-traumatic stress disorder (PTSD), particularly its war-related subtype.
Methods: A comprehensive search of PubMed, Scopus, and Web of Science was conducted using keywords related to PTSD, gene expression, and DNA methylation. Studies published between 2000 to 2024 involving adult military personnel with confirmed PTSD based on the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria were included. Animal studies, psychological interventions, and pharmacological research were excluded. Only cross-sectional, case-control, or cohort studies utilizing blood, saliva, or brain tissue samples were considered. Data from 28 studies were extracted using a predefined framework, focusing on population characteristics, study design, and identified hub genes.
Results: Key findings revealed the upregulation of immune-related genes (e.g., CCL4, NF-κB) and hypomethylation of inflammation-related genes. Downregulation of neurodevelopmental genes, such as Brain-Derived Neurotropic Factor (BDNF) and Down syndrome cell adhesion molecule (DSCAM), highlighted disruptions in synaptic plasticity. The identified pathways suggested potential biomarkers and therapeutic targets for precision medicine approaches.
Conclusion: This review highlighted the role of gene expression alterations in war-related PTSD. The identified genes might serve as candidates for personalized therapies. Further research is required to validate these findings and develop targeted interventions.

Keywords: Post-traumatic stress disorder, Genomics, Combat disorders.

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Introduction

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that develops as a result of exposure to life-threatening and traumatic events, such as war, natural disasters, violence, or accidents. Symptoms include intrusive thoughts, physiological changes, nightmares, and flashbacks [1, 2]. Among different subtypes of PTSD, combat-related trauma exhibits unique gene expression patterns, immune dysregulation, and molecular signatures. For example, Logue *et al.,* [3] highlighted that the wound-healing module, which was downregulated in men exposed to combat trauma, differed from pathways activated in cases of interpersonal trauma.

The lifetime prevalence of PTSD in U.S. veterans was 6.9%, with rates as high as 20% among war veterans [4]. Factors contributing to the high prevalence of PTSD in this population included the nature of conflict, the duration of exposure to life-threatening situations, and the severity of injuries sustained during service [5]. Initial estimates suggested that 30% of Vietnam War veterans developed PTSD, but reanalysis indicated a lifetime prevalence of 19 [6]. A decade after the war, 28% of veterans with a history of combat exposure were diagnosed with PTSD. Recent studies highlighted a direct relationship between PTSD prevalence and combat exposure, with an average prevalence of 6% across population samples from various countries and services. The number of PTSD cases among veterans of the Afghanistan and Iraq wars has risen to over 20%, underscoring the need to understand the environmental and genetic mechanisms underlying this disorder [6].

Twins and heritability studies among military personnel showed that 30-70% of PTSD risk variability could be attributed to genetic factors depending on the type of trauma experienced [7, 8]. Advances in transcriptome and gene expression studies have provided new insights into PTSD, but the functional roles of these genetic changes remain poorly understood. Identifying the association between genetic variations and treatment outcomes could reveal novel therapeutic targets. Military personnel and soldiers, due to their frequent exposure to high-stress environments, represent a critical population for PTSD research. The epigenome can adapt to environmental influences through chemical modifications to proteins and chromatin, leading to long-lasting changes in gene expression and regulation. Most epigenetic studies on PTSD have primarily focused on DNA methylation, a key epigenetic process.

Recent hypothesis-free genome-wide, epigenome-wide, and transcriptomic studies have identified several genes associated with immune system functioning, highlighting their potential role in PTSD [9]. However, the specific gene pathways and mechanisms that determine vulnerability or resilience to PTSD following trauma remain largely unexplored [10].

This systematic review and computational analysis aimed to identify hub genes and key pathways involved in combat-related PTSD, with a focus on DNA methylation and gene expression. By deepening our understanding of the epigenetic and transcriptome processes underlying PTSD, this study aimed to identify actionable therapeutic targets and improve treatment outcomes for war veterans.

Materials and Methods

This systematic literature review was conducted in accordance with the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11].

Search Strategy

A comprehensive and systematic search was performed across PubMed, Scopus, and Web of Science databases using the following keywords and Boolean operators:

((“Post-Traumatic Stress Disorder”[MeSH Terms] OR “PTSD” OR “Posttraumatic Stress Disorder” OR “Post Traumatic Stress Disorder”) AND (genetic association [MeSH Terms] OR polymorphism [MeSH Terms] OR genotype [MeSH Terms] OR “gene” OR “genetic” OR “epigenetic” OR “methylation” OR “genetic” OR “genogroup” OR “SNP” OR “single nucleotide polymorphism” OR “single-nucleotide polymorphism”)). All items were detailed in the search strategy figure (Figure 1)

The search was restricted to studies published between 2000 and January 2024, as epigenetic research has gained prominence in the 21st century with the advent of modern assessment techniques. Prior to 2000, most studies relied on targeted candidate gene analysis using qPCR, often with limited sample sizes and lacking the advanced microarray technologies available today [12, 13].

Inclusion and Exclusion Criteria

This review included original research papers. The review articles were excluded due to their lack of primary data and subjective nature. Peer-reviewed studies were prioritized, while clinical trials were excluded because of the significant impact of interventions on genomic data. Animal studies were also excluded due to challenges in generalizing findings on gene expression and DNA methylation processes from animals to humans. Studies involving adult military personnel with confirmed PTSD, diagnosed according to standardized criteria, were included. Eligible study designs included cross-sectional, case-control, and both retrospective and prospective cohort studies. Participants with a history of substance abuse or traumatic brain injury (TBI) were excluded, as these factors could confound DNA methylation and gene expression patterns [14, 15]. The PRISMA flowchart detailing the study selection process is presented in Figure 1.

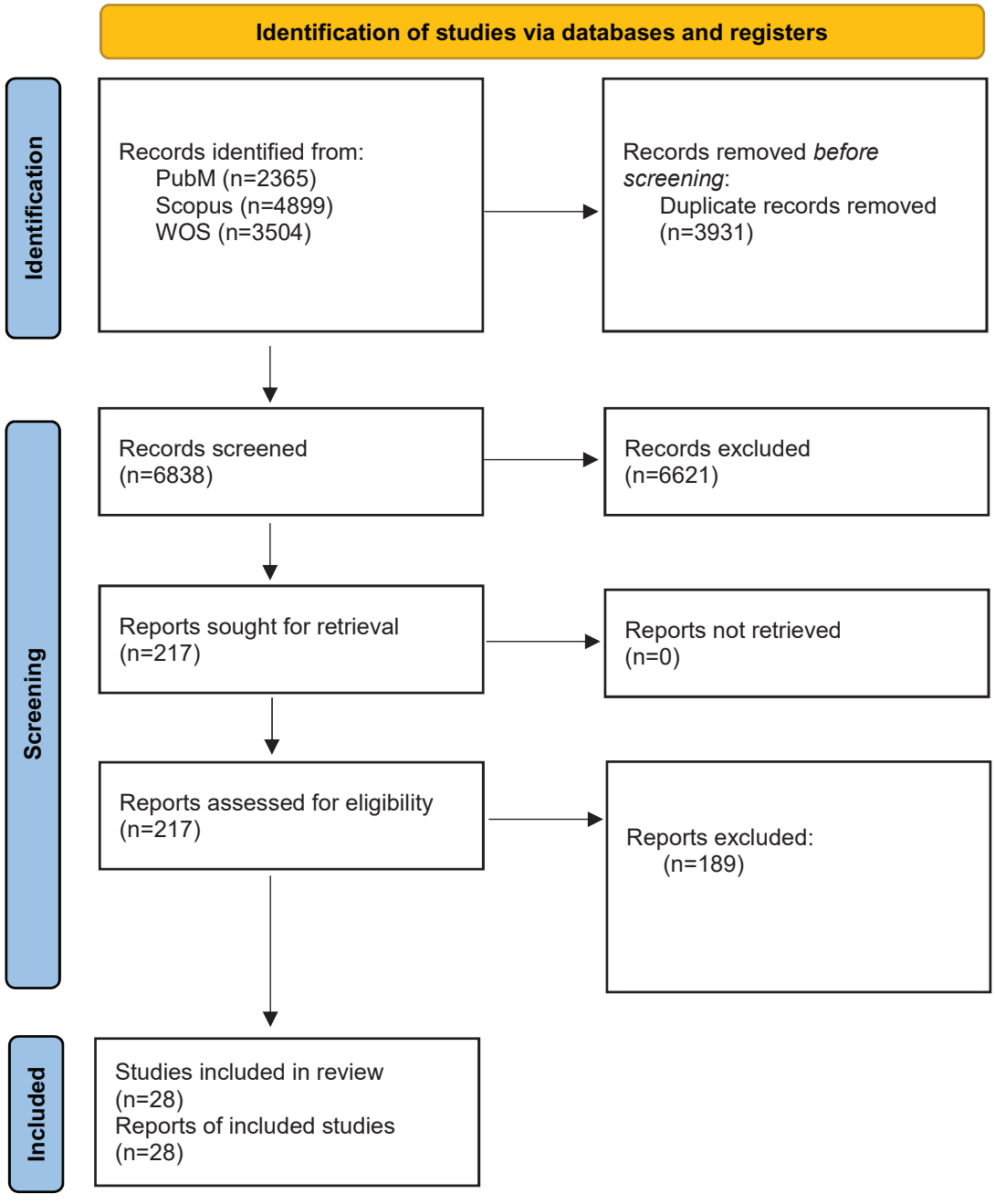

Fig. 1. PRISMA flowchart of the selected studies

Confirmation of PTSD

PTSD diagnosis was confirmed using the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria. Although comorbid psychological conditions such as depression and alcohol dependence often co-occur with PTSD, they were excluded from this review as they fall outside its scope. In studies examining multiple psychological outcomes, only findings related to PTSD were considered.

Genomic Outcomes

This review focused on gene expression and DNA methylation patterns. Other genomic or epigenetic pathways, such as genotyping, polymorphism research, histone modification, and epigenetic aging, were excluded. All tissue types used for DNA methylation analysis, including blood and saliva samples, were considered. However, studies examining epigenetic or gene expression changes resulting from psychological interventions or pharmacological treatments were excluded.

Study Selection and Data Extraction

Search results were exported into Rayyan, a systematic review tool, to streamline the selection process, manage duplicate articles, and maintain a record of the screening process [16]. The full texts of the identified articles were carefully assessed for adherence to the predefined inclusion criteria. Disagreements during the selection process were resolved through discussion among reviewers. Data

were extracted using a predefined data extraction sheet in Microsoft Excel. The following data were extracted from the included studies: author, year of publication, study design, population characteristics, genetic findings, and identified hub genes. Extracted variables also included, but were not limited to these key elements. To assess the validity of the studies, the authors independently evaluated the risk of bias, focusing on the completeness of outcome data and addressing issues such as participant exclusions, attrition, and incomplete outcome data. This study adhered to ethical standards for the analysis of secondary data. No ethical approval was required, as the research utilized publicly available data.

Results

The systematic review included 28 studies (n=2,677 cases and 4,901 controls) [3, 6, 8, 17-40] investigating gene expression and epigenetic changes in PTSD. The studies primarily employed case-control, cohort, or cross-sectional designs and involved diverse populations, including veterans, military personnel, and trauma-exposed civilians, with a predominance of male participants. Blood samples were the most commonly used biological material for gene expression and methylation analysis.

Among the included studies, 14 focused on DNA methylation, 9 on gene expression, and 6 on both. The study designs comprised 12 case-control studies, 4 cross-sectional studies, and 12 cohort studies. Geographically, 15 studies were conducted in the U.S., 3 in Australia, 3 in the Netherlands, 2 in Serbia, and 1 each in Canada, Germany, and South Korea. Veterans and controls were predominantly men, with some studies excluding female participants entirely. Participant ages ranged widely, with most individuals between 20 and 70 years. All studies utilized blood samples except for Montalvo-Ortiz *et al.,* which examined saliva and postpartum brain samples [30].

The studies collectively highlighted the multifaceted nature of PTSD, driven by immune dysregulation, altered neuroplasticity, and accelerated aging. The identification of biomarkers and pathway-specific targets paved pathways for precision medicine approaches, highlighting the need for continued research to validate these findings and develop tailored interventions. A comprehensive Table 1 provides detailed characteristics of the included studies, including the country of study, sample sizes (cases and controls), source of biological samples, PTSD diagnostic criteria, differentially expressed genes (upregulated, downregulated, hypermethylated, or hypomethylated), key findings, and limitations. Specific focus was placed on the upregulation or downregulation of genes and their associated pathways, such as immune response and stress regulation, to identify patterns across studies. The extracted data included the proportion of hypomethylated and hypermethylated genes and their potential relevance to PTSD severity and progression.

Table 1. Summary of the main findings of the included studies.

Author / year (ref)	Study Type	Country	Members	Patients		Controls		Sample	Genes	Key Findings
				All	Male	All	Male			
Crombach A / 2024 [22]	Longitudinal study	Germany	Active-duty Burundian soldiers	191	All Male	NA	NA	Blood Sample	**Hypermethylated** *PLA2G4A PLA2G4B JMJD7 PLA2G1B* **Hypomethylated** *ALOX15*	Differential methylation of genes in the linoleic acid metabolism pathway was significantly associated with PTSD symptom severity. This pathway's involvement highlights potential epigenetic mechanisms mediating memory and stress responses.
Wani AH / 2024 [41]	Cohort	USA	Five diverse cohorts, including both civilian and military participants	314	(1.05) Total ratio	912	(1.05) Total ratio	Blood Sample	**Hypomethylated** *DYNC1H1 RAMP3 AP2B1 DAZAP2* **Hypermethylated** *CREBZF*	Identified methylation markers such as FADS1 and GYTL1B associated with PTSD severity. *DYNC1H1, RAMP3, AP2B1,* and *DAZAP2* were hypomethylated in PTSD patients, except for *CREBZF*, which was hypermethylated.

Author / year (ref)	Study Type	Country	Members	Patients		Controls		Sample	Genes	Key Findings
				All	Male	All	Male			
Montalvo-Ortiz/ 2022 [30]	Cohort	USA	Military veterans participated in the National Health and Resilience in Veterans Study (NHRVS)	Current PTSD: 34	All male	Current PTSD: 1101	All male	Saliva	**Upregulated** *DYNC1H1* *RAMP3* *AP2B1* *DAZAP2* Downregulated *CREBZF*	All genes were hypomethylated, except for *CREBZF* and, *SENP7* in postpartum brain samples.
				Lifetime PTSD: 65	All male	Lifetime PTSD: 1070	All male		**Upregulated** *GTF2IRD1* CD55 SENP7 Downregulated SENP7 (Postmortem brain tissue from OFC)	
Young/ 2021 [42]	Case-Control	Australia	Australian Vietnam veterans	All: 159 Genome analysis: 48	All male	All: 140 Genome analysis: 48	All male	Whole blood	**Upregulated** *AIM2*	Veterans with PTSD had significantly higher CRP levels and decreased *AIM2* gene methylation compared to controls while no significant difference in CRP genotype counts.
R Yang / 2021 [6]	Cohort	USA	Combat trauma-exposed male veterans	83	All Male	83	All Male	Blood Sample	**Hypermethylated** *CST3* *PAI-1* *TIMP-1*	According to the study, men with PTSD who have experienced war trauma had higher AgeAccelGrim values, which suggests that their biological aging has accelerated. The PTSD group had significantly higher levels of four DNA methylation surrogate indicators, which are associated with age-related health issues like inflammation and cardiovascular diseases: cystatin C, PAI-1, TIMP1, and smoking pack-years.
Van der Wal/ 2020 [35]	Cohort	Netherlands	Dutch military personnel deployed to Afghanistan for at least four months	All: 125/ Resilient: 74/ Recovering: 19/ Delayed onset: 32	All: 92.8%/ Resilient: 94.6%/ Recovering: 89.5%/ Delayed onset: 90.06%	--	--	Whole blood	Upregulated *DMR1* *TUBA3FP* *P2RX6* *DMR2* EP300 miRNA 1281 (Delayed onset PTSD trajectory compared to a resilient profile) *DMR7* **Downregulated** DMR6 IMPA1 (a delayed onset PTSD trajectory compared to a recovering; one- and six-months post-deployment)	Fourteen genomic regions were identified in which PTSD symptom levels were associated with methylation changes over time (pre-deployment, one-, and six months post-deployment).

Author / year (ref)	Study Type	Country	Members	Patients		Controls		Sample	Genes	Key Findings
				All	Male	All	Male			
Wolf / 2020 [43]	Cross-sectional	USA	Non-Hispanic military veterans	309	289/ 20	No control	No control	Blood Sample	Hypermethylated KL	*KL* methylation inversely correlates with CRP, a marker of systemic inflammation. CRP levels were used as a biomarker for inflammation-related biological aging. The association between PTSD and CRP levels is mediated by *KL* methylation, highlighting its role in stress-related inflammation and aging.
Kang / 2019 [27]	Cohort	South Korea	South Korean veterans during the Vietnam War	123	All Male	116	All Male	Blood Sample	**Hypermethylated** *FKBP5*	The study found that the T allele of rs1360780 was associated with lower *FKBP5* methylation levels, and the PTSD group showed significantly higher methylation than the non-PTSD group among veterans carrying the risk T allele. No difference was observed in methylation levels among veterans with the CC genotype. *FKBP5* methylation levels were positively correlated with PTSD symptoms among T allele veterans.
Voisey J / 2019 [37]	Case-control	Australia	Male Vietnam veterans	48	All Male	48	All Male	Blood Sample	**Hypermethyled** *BDNF*	PTSD was associated with increased *BDNF* methylation at three CpG sites, correlating with increased PTSD symptom severity. Active exercise was linked to lower methylation levels at these sites, suggesting exercise may modulate *BDNF*-related pathways and benefit PTSD treatment.
Heather L Rusch2019 / [31]	Case-control	USA	US military service members	39	All Male	27	All Male	Whole blood	Upregulated *C5orf24* *RBAK* *CREBZF* *CD69* *PMAIP1* *AGL* *ZNF644* *ANKRD13C* *ESCO1* *ZCCHC10*	All these genes are upregulated in participants with high intrusion symptoms. Most downregulated genes are associated with symptom improvement. NF-kB was downregulated with symptom reduction.

Author / year (ref)	Study Type	Country	Members	Patients		Controls		Sample	Genes	Key Findings
				All	Male	All	Male			
Divya Mehta/ 2018[44]	Cross-sectional	Australia	Australian Vietnam War veterans	48	All Male	48	All Male	Blood samples	**Downregulated** *MS4A15* *MLPH* *GUCA2A* *LOC100128998* *LOC642344* *ARMC6* *LOC402509* *TMEM217* *C22orf30* *USP24* *CHRAC1* *LOC643402* **Upregulated** *LOC100131989* *PCDHB9* **Hypermethylated** *C8orf37* *EEF1A1* *FAM40B* *RPL14* *RUNDC2C* *SPTLC1* *TMEM217* *USP49* *VPS41*	49% of the differentially expressed genes also exhibited changes in DNA methylation. The study highlighted the enrichment of genes involved in immune response pathways, such as cytokine-cytokine receptor interaction, Jak-STAT signaling, and Toll-like receptor signaling.
Miller/ 2018 [29]	Case-control	USA	US military veterans deployed on post-9/ 11 operations to Iraq and/ or Afghanistan	163	87.10%	123	90.20%	Whole blood	Upregulated AIM2	The positive correlation between serum CRP was mediated by methylation at the AIM2 locus. rs3091244, a functional SNP in the CRP promoter region moderated the association between lifetime trauma exposure and current PTSD severity.
Boscarino/ 2018 [20]	Case-control	Canada	Canadian Armed Forces infantry soldiers returning from deployment in Afghanistan	27	All male	58	All male	Whole blood	**Upregulated** *LRP8* *GOLM1* *LINC00943* LOC1001322 15 **Downregulated** *CYP2C8*	PTSD symptoms were associated with increased expression of *LRP8* and *GOLM1* and decreased expression of *CYP2C8* in peripheral blood samples.

Author / year (ref)	Study Type	Country	Members	Patients		Controls		Sample	Genes	Key Findings
				All	Male	All	Male			
Ham-mamieh/ 2017 [25]	Case-control	USA	Combat veterans from Operation Enduring Freedom (OEF)/ Operation Iraqi Freedom (OIF)	79 (48 in training set and 31 in test set)	All male	80 (51 in trainig test and 29 in testing test)	All male	Whole blood	**Upregulated** DMRTA2 ELK1 GATA3 NFATC4 PTTG1IP **Downregulated** *AKT1* *BDNF* *CNR1* *CREB1* *EFS* *ETS-2* *HES4* *LHX1* *MET* *NR2E1* *PAX5* *PDGFB* *PSD* *TRERF1*	Most CpG islands (84.5%) were hypermethylated in PTSD patients. Functional networks associated with PTSD include nervous system development, endocrine signaling, and somatic complications like inflammation and circadian rhythm dysregulation.
Bam M / 2017[17]	Case-control	USA	War veterans	8	All Male	4	All Male	Blood Sample	**Upregulated** *JAK2* *STAT1* *IL23A* *TGFB1* *TGFB2* *TGFB3* *T-BET* **Downregulated** *AGO2* *DCR1* Several miRNAs (specific miRNAs not listed)	Reduced expression of *AGO2* and *DCR*1 in PTSD PBMCs leads to diminished miRNA biogenesis, contributing to elevated inflammation through dysregulated gene expression. *STAT3* was identified as a regulator of *AGO2* and *DCR1*, and its reduction further exacerbated the dysregulation.
Bam M / 2016[45]	Cross-sectional	USA	War veterans	miRNA microarray=8 RNA-Seq=5	All Male	4 for miRNA microarray; 5 for RNA-Seq	All Male	Blood Sample	**Upregulated** *GZMB* *CXCL3* *STAT4* **Downregulated** *MTRNR2L1* *MMP25* *CXCL8* *G0S2* **Hypermethylated** CSRNP1 **Hypormethylated** 12 genes had decreased DNA methylation	Dysregulated immune system pathways in PTSD were associated with altered miRNA expression and DNA methylation, highlighting their role in systemic inflammation observed in PTSD.

Author / year (ref)	Study Type	Country	Members	Patients		Controls		Sample	Genes	Key Findings
				All	Male	All	Male			
Boks/ 2016 [19]	Cohort	Netherlands	Dutch soldiers deployed to Afghanistan	1. High trauma high PTSD symptom: 32 2. High trauma, low PTSD symptom: 29 3. Low trauma low PTSD symptoms: 32 4. All: 93	All male	--	--	Whole blood	**Downregulated** *SKA2*	Decreases in *SKA2* methylation post-deployment were associated with PTSD development. Increased SKA2 methylation was linked to exposure to traumatic stress without developing PTSD. *SKA2* methylation predicted PTSD development, especially when combined with childhood trauma history.
Logue/ 2015 [46]	Cohort	USA	Trauma-exposed white non-Hispanic veterans	115	All male	28	All male	Whole blood	Upregulated *TBC1D15* **Downregulated** *DSCAM* *ATP6AP1L* *NR3C1* *BDNF TXNRD1*	All but *TBC1D15* had lower expression in PTSD. The most significant was *DSCAM*, a neurological gene expressed widely in the developing brain, amygdala, and hippocampus of the adult brain. **Biological Pathways Implicated** • **HIF**: Related to cellular response to stress. • **mTOR** Implicated in cellular growth and metabolism. • **Insulin** Linked to metabolic effects
Sadeh/ 2015 [33]	Cohort	USA	White non-Hispanic veterans from recent conflicts	200 Current PTSD: 116	91%	--	--	Whole blood	**Downregulated** *SKA2 (rs7208505)*	Increased *SKA2* methylation is associated with reduced cortical thickness in key prefrontal regions and higher PTSD symptom severity.

Author / year (ref)	Study Type	Country	Members	Patients		Controls		Sample	Genes	Key Findings
				All	Male	All	Male			
Pedro Guardado/ 2015 [24]	Observational study	USA	Active duty U.S. military personnel	28	27/ 28	27	26/ 27	Blood samples	**Upregulated** *CCL4* *TLRs* *NF-κB* *MAPK* *IL-1B* *TNF* *IL-6* *DNMT3B HDAC6* **Downregulated** *GFI1* *IGF1R* *PER1* *MGAT4A* *TARP* *GH* *CDC14A, ZNF831* *IL13* *ITCH* *HSPD1* *SYNE2* **Hypomethylated** DNMT3B	The study indicates dysregulation in genes related to innate immune responses, neuroendocrine functions, and NF-kappa B systems, which may inform future pharmaceutical interventions for PTSD.
Yehuda/ 2015 [40]	Case-control	USA	Vietnam, Iraq, or Afghanistan veterans	61	All male	61	All male	Whole blood	Upregulated NR3C1-1F	PTSD veterans exhibited lower *NR3C1-1F* promoter methylation compared to controls. Lower methylation was correlated with higher glucocorticoid receptor sensitivity and altered neuroendocrine functions.
Daniel S / 2015[34]	Prospective cohort	USA	U.S. Marines	25	All Male	25	All Male	Blood Sample	**Downregulated** *GSTM1* *GSTM2* *C1orf50* *F2R* *TBC1D4* *RPL10A AHNAK* *PINK1. MAGEA1* *OLFML2A* *NBPF3* *EIF4B* *RP9* PSPH	A blood-based biomarker panel could predict PTSD with 80–90% accuracy, highlighting the role of immune-related genes and dysregulated oxidative stress pathways.

Author / year (ref)	Study Type	Country	Members	Patients		Controls		Sample	Genes	Key Findings
				All	Male	All	Male			
Rusiecki/ 2013 [32]	Case-control	USA	Army and Marines service members serving their first OEF/ OIF deployment	74	66.2%	74	66.2%	serum	upregulated *IGF2* *IL16* *IL8* Downregulated *IL18* *H19*	increased *IL18, H19* methylation post-deployment. Stratified analyses revealed more pronounced differences in the adjusted means of pre-post *H19* and *IL18* methylation differences for cases versus controls among older service members, males, service members of white race, and those with shorter deployments (6–12 months).
Hollifield/ 2013 [26]	Case-control	USA	Military personnel in Albuquerque with significant combat exposure in Iraq or Afghanistan	6	All male	11	N=7	Whole blood	**Upregulated** *TNFRSF10B* *IL10RB* *IL16* *IL4R*	Inflammatory disinhibition may be involved in combat-induced PTSD and may be responsible for the increased prevalence of inflammatory-related illnesses observed in PTSD.
Gordana Matić/ 2013 [47]	Cross-sectional	Serbia	Male veterans who were recruited in Serbia	Current PTSD=113, With life-time PTSD=61	All Male	88	All Male	Blood Sample	**Downregulated** *FKBP5 STAT5B*	Current PTSD patients exhibited reduced glucocorticoid hormone-binding potential and a diminished correlation between binding sites (Bmax) and hormone affinity (KD). In contrast, trauma controls had higher binding potential compared to current PTSD patients.
Glatt SJ / 2013[23]	Prospective cohort	USA	U.S. Marines	25	All Male	25	All Male	Blood Sample	**Downregulated** *SUV420H1* *TMEM191A* *RPL39* *AGPHD1* *RPL10A. CA13* *PARD6B*	Gene expression profiles in peripheral blood pre-deployment can predict PTSD with up to 80% accuracy using exon-based biomarkers. Dysregulation in immune and inflammatory pathways was observed in individuals who later developed PTSD. All genes decreased expression.

Author / year (ref)	Study Type	Country	Members	Patients		Controls		Sample	Genes	Key Findings
				All	Male	All	Male			
van Zuiden/ 2011[36]	Cohort	Netherlands	Male soldiers	35	All Male	413	All Male	Blood Sample	**Downregulated** *FKBP5* **Upregulated** *GILZ* *SGK1* *GR*	Pre-deployment GR pathway components are vulnerability factors for subsequent development of a high level of PTSD symptoms. Downregulation of *FKBP5* mRNA predicted an increased risk of developing a high level of PTSD symptoms.
Brkljačić 2010/ [21]	Case-control	Serbia	---	All=14 Current PTSD=7 Lifetime PTSD=7	All Male	All= 14 Current PTSD=7 Lifetime PTSD=7	All Male	Blood Sample	*BA* *GAPDH* *B2M* *PolR2A*	*GAPDH, B2M*, and *BA* as reference genes for accurate gene expression quantification in PBMCs from war veterans with and without PTSD.

CRP C-Reactive Protein. CpG Cytosine-phosphate-Guanine. miRNA MicroRNA. OFC Orbitofrontal Cortex. NHRVS National Health and Resilience in Veterans Study. OEF Operation Enduring Freedom. OIF Operation Iraqi Freedom. PTSD Post-Traumatic Stress Disorder. PBMCs Peripheral Blood Mononuclear Cells. SNP Single Nucleotide Polymorphism.

The key findings include:

a. Alterations in Gene Expression

Studies reported significant gene expression changes associated with PTSD, highlighting dysregulation in immune, inflammatory, and neurodevelopmental processes:

i. Immune Response and Inflammation

Mehta *et al.,* [8] identified 60 differentially expressed genes (DEGs), with enrichment in the cytokine-cytokine receptor interaction and Janus kinase-signal transducer and activator of transcription (JAK/STAT) signaling pathways. Guardado *et al.,* reported significant upregulation of C-C motif chemokine ligand 4 (*CCL4*) with a fold change of 3.39, along with other inflammatory mediators such as nuclear factor kappa-light-chain-enhancer of activated B cells (*NF-κB*), tumor necrosis factor (*TNF*), and interleukin (*IL-6*). Rusch *et al.,* [31] found that cluster of differentiation (CD69) was upregulated in individuals with severe PTSD symptoms, further implicating immune activation. Rusiecki *et al.,* demonstrated the upregulation of *IL-8* and *IL-16*, which were associated with neuroinflammation and act as chemoattractants for immune cells expressing surface CD4 molecules, respectively [32]. In contrast, they reported downregulation of *IL-8*, which induced interferon-gamma (IFN-γ) and facilitated its passage through the blood-brain barrier. Logue and colleagues observed lower expression of thioredoxin reductase 1 (TXDR1), which induced an anti-oxidant response [3]. Hollifield *et al.,* reported the upregulation of several immune-related genes, including TNFRSF10B and IL-4R, both of which were involved in pro-inflammatory regulation [26].

i. Neuroplasticity and Neurodevelopment

Logue *et al.,* observed reduced expression of genes such as Down syndrome cell adhesion molecule (*DSCAM*) and Brain-Derived Neurotropic Factor (*BDNF*), both of which are critical for neural development and synaptic plasticity [3]. Matić *et al.,* [23] and Zuiden *et al.,* [36] reported decreased expression of FKBP5, consistent with hypothalamic pituitary adrenal (HPA) axis dysregulation and increased stress vulnerability. Increased glucocorticoid receptor (GR) numbers [36] further indicated heightened glucocorticoid receptor sensitivity. Consistently, Hollifield *et al.,* [26] demonstrated upregulation of *IL16*, which was regulated by *GR*.

ii. Pro-inflammatory Markers

Bam *et al.,* [17] identified elevated levels of pro-inflammatory genes such as Janus kinase 2 *(JAK2)* and Signal Transducer And Activator Of Transcription 1 *(STAT1)*. Meanwhile, downregulation of microRNA (miRNA) biogenesis genes, such as Argonaute RISC Catalytic Component 2 *(AGO2)* and Decoy Receptor 1 *(DCR1),* suggested disrupted post-transcriptional regulation.

b. Epigenetic Modifications

Epigenetic alterations, particularly DNA methylation, were consistently associated with PTSD.

i. Methylation Patterns

Hypomethylation of genes such as Doublesex and Mab-3-related Transcription Factor A2 *(DMRTA2)* and *ELK1* disrupted synaptic and immune functions. Similarly, Wani *et al.,* [38] identified methylation markers such as *FADS1* and *GYTL1B* associated with PTSD severity. *DYNC1H1, RAMP3, AP2B1,* and *DAZAP2* were hypomethylated in PTSD patients, while CREBZF, was hypermethylated [30]. Gene SUMO Specific Peptidase 7 *(SENP7),* involved in stress response in T-cells, showed a hypomethylation pattern in the saliva sample of patients with lifetime PTSD; however, the postpartum brain tissue sample showed downregulation [30]. Veterans with PTSD exhibited decreased methylation of *AIM2*, which correlated with increased C-reactive protein (CRP) levels and indicated inflammatory responses [28, 29]. Methylation of *TUBA3FP, P2RX6*, and *IMPA1* was linked to delayed-onset PTSD, suggesting roles in memory and cognition-related pathways [35]. In PTSD patients, Hammamieh *et al.,* [25] reported hypermethylation in 2,401 genes, consisting of 84.5% of DNA sequences in which cytosine and guanine were linked by phosphate (CpG islands), including genes such as AKT Serine/Threonine Kinase 1 *(AKT1)*, BDNF, Cannabinoid receptor 1 *(CNR1)*, and CAMP Responsive Element Binding Protein 1 *(CREB1)*, which were involved in the nervous system and inflammation pathways [25]. The decreased methylation of Spindle and Kinetochore Associated Complex Subunit 2 *(SKA2*) was associated with PTSD development, particularly in individuals with a history of trauma in childhood [19, 33]. The *NR3C1* promoter in PTSD patients had lower methylation, with increased sensitivity of glucocorticoid receptors and disturbed neuroendocrine functions [40]. Increased methylation of *IL-18* and *H19* was seen in PTSD patients after deployment, highlighting the importance of immune regulation and stress response [32]. Furthermore, Boscarino *et al.,* found hypomethylation of *LRP8*, and *GOLM1*, which mediated synaptic plasticity and memory formation in PTSD patients [20].

ii. Exercise-induced Methylation Changes

Voisey *et al.,* [37] highlighted the role of physical activity in reducing BDNF methylation levels, suggesting exercise as a potential modulator of PTSD-related epigenetic changes.

c. Biological Pathways

Disruption of critical pathways underscored the complexity of PTSD pathophysiology:

Stress and Immune Pathways

Dysregulation in glucocorticoid signaling pathways was evident, with altered expression of *FKBP* Prolyl Isomerase-5 (*FKBP-5*) and *GR* [23, 36, 40]. The *NR3C1* (glucocorticoid receptor) gene, which encodes the glucocorticoid receptor, was associated with glucocorticoid sensitivity and neuroendocrine responses. Hypomethylation of the *NR3C1* promoter was associated with altered stress responses and PTSD symptoms [3, 40].

The *SKA2* gene was found to regulate cortisol feedback inhibition through the Hypothalamic-Pituitary-Adrenal (HPA) axis, with methylation changes influencing stress susceptibility and PTSD development [19, 33]. Hyper- and hypomethylation of genes such as *IL-8*, *IL-16*, and *IL-18* reflect dysregulated immune responses in PTSD, with these interleukins playing roles in inflammation and neuroinflammation [25, 28, 29, 32]. *AIM2* methylation changes were linked to increased systemic inflammation and innate immune activation, suggesting its role in PTSD pathogenesis [28, 29].

i. Linoleic Acid Metabolism

Crombach *et al.,* linked altered methylation in linoleic acid metabolism genes to PTSD, suggesting its impacts on memory, immune regulation, and stress resilience [22].

ii. Pro-inflammatory Pathways

Bam *et al.,* [17] emphasized the upregulation of JAK/STAT, *IL-23A*, and Tumor Growth Factor-β (*TGF-β*) pathways, reinforcing their role in PTSD-associated inflammation.

Discussion

This review of 28 studies explored gene expression and epigenetic changes, particularly DNA methylation, in combat-related PTSD, highlighting immune dysregulation, altered neuroplasticity, potential biomarkers, and therapeutic targets.

a. Immunity dysregulation and Inflammation

Immune dysregulation in PTSD could lead to chronic stress responses, increased inflammation, and altered cytokine activity, all of which significantly contribute to the pathophysiology of PTSD [48, 49]. Analyses of immunological markers showed elevated plasma levels of pro-inflammatory cytokines, such as IFN-γ, IL-6, TNF-α, and IL-17, as well as increased levels of immune-stimulating Th1 cells and inflammatory Th17 cells in PTSD patients, indicating a pro-inflammatory-state-and-impaired immune balance [50]. Changes in the methylation levels of some gene promoters (e.g., IL-12b, and IFN-γ) in peripheral blood monocytes can cause a rise in inflammatory cytokines (e.g., IL-12) in PTSD patients [18]. Traumatic events might also weaken the immune system by altering gene expression [48]. Inflammatory processes increase susceptibility to psychological stress, thereby elevating the risk of developing PTSD [48, 49, 51]. Dysregulated immunological pathways, including the overexpression of pro-inflammatory genes (e.g.,

CCL4, NF-κB, and TNF), highlighted the significant role of systemic inflammation in PTSD [31]. The findings of this study suggested that alterations in DNA methylation and the activity of genes such as *CD55, DAZAP2, AHRR, CDC42BPB, DOCK2, EP300,* and *P2RX6* could influence immune responses and inflammatory processes, increasing an individual's susceptibility to psychological stress, and ultimately increased the risk of PTSD. Therefore, a detailed understanding of these pathways and their interactions was crucial for developing new diagnostic and therapeutic approaches for PTSD.

Methylation of *CD55* and *DAZAP2* could alter the balance of cytokine activity and the regulation of immune responses. For instance, hypermethylation in the *CD55* gene might result in inflammation increased by reducing its regulatory role in complement inhibition [30]. *DAZAP2* plays a key role in immune signaling pathways, such as *NF-κB* and *JAK/STAT*, regulating inflammation and immune responses, and modulating the function of immune cells, such as macrophages, T cells, and B cells [52]. Hypermethylation of the *DAZAP2* promoter regions decreased its expression in individuals with combat-related PTSD, leading to immune dysregulation and chronic inflammation [30, 38]. Systemic inflammation resulting from *DAZAP2* alterations could elevate levels of CRP, a marker of chronic inflammation in PTSD [38]. Long-term inflammation might exacerbate PTSD-related neurological disorders, such as memory problems and anxiety [8]. Therefore, since this gene plays a role in modulating the immune system in different ways, it can be a therapeutic target for PTSD. However, the lack of extensive studies directly investigating *DAZAP2* changes in PTSD, particularly in combat veterans, and the complexity of its associated pathways and interaction with other genes highlighted the necessity for future research to explore its potential therapeutic targets.

The association between the immune system and PTSD was supported by the discovery of three CpGs (*cg05575921*, *cg21161138*, and *cg23576855)* in AHRR [39, 53], a gene involved in immunomodulation, including T lymphocyte regulation, B cell maturation, and the activity of macrophage, dendritic cell, and neutrophils. Downregulation of *AHRR* could cause excessive immune response and cytokine release, such as IL-6 and TNF-α, which were consistent with the onset and exacerbation of PTSD symptoms [54]. Hypermethylation of the *CDC42BPB* gene, which is involved in cytoskeletal rearrangement, cell migration, and neurodevelopment, was linked to PTSD and associated with depressive symptoms [55] and increased CRP levels [4], suggesting inflammation as a key component of PTSD [38, 56]. Hypomethylation of the *AIM2* gene, involved in innate immunity, was also associated with increased CRP levels in veterans with PTSD [28]. Future research should investigate *CDC42BPB* and *AIM2* methylation as mediators in the relationship between PTSD and inflammation, as well as the role of CRP as a diagnostic marker and potential therapeutic target. The upregulation of *IL-10RB, IL-16, and IL-4R* genes, which play crucial roles in immune modulation, leads to inflammatory disinhibition and immune dysregulation in combat-induced PTSD [26]. *IL-10RB* controls mucosal immune tolerance and anti-inflammatory macrophage activity [57], while *IL-4R* stimulates cell proliferation, tissue regeneration, and neurological functions [58]. IL-16 regulates T-cell growth, activation, and motility [59]. Dysregulation of these immunological signaling pathways is a hallmark of PTSD, exacerbating neuroinflammation, and anxiety-like behaviors [26].

b. Pro-inflammatory markers

TBX21 and *STAT4* play crucial roles in regulating T cell activity. *TBX21* controls the transcription of interferon-gamma (IFN-γ), a pro-inflammatory gene upregulated in PTSD. Furthermore, the expression of pro-inflammatory cytokines, such as *CCL4, CCL5, CXCL1, CXCL2, CXCL3, CXCL6,* and *CXCL8* is generally altered in PTSD. These findings suggested that shifts in T cell biology are a primary driver of the underlying inflammation observed in PTSD [17].

Several potential biomarkers and immune therapeutic implications emerged from the studies. For instance, Guardado *et al.,* [24] and Mehta *et al.,* [8] highlighted the upregulation of immune-related genes such *as CCL4* and *CD69* as diagnostic markers, while inflammatory markers such as CCL4 and NF-κB point to immune-modulating therapies. Due to the high costs of measuring gene expression, downstream molecules such as microRNAs (miRNAs) or proteins encoded by these genes might serve as practical diagnostic biomarkers and therapeutic options. For instance, *hsa-miR-193a-5p and hsa-miR-125a*, which target the pro-inflammatory cytokines interleukin-12B (*IL12B*) and interferon-gamma (IFNG), respectively, were downregulated in PTSD [17, 18]. Additionally, Bam *et al.,* identified several miRNAs that were predicted to target *TBX-21* and *STAT4*, key genes in the Th cell differentiation pathway [17]. Therefore, these miRNAs represent potential diagnostic or therapeutic biomarkers for veterans with PTSD.

However, implementing these diagnostic and therapeutic methods presents certain challenges. One of the major limitations of anti-inflammatory and anti-immune therapies in PTSD patients is the heterogeneity in molecular pathways and immune responses, which renders standard treatment approaches ineffective for all individuals. The complex interference and interactions of inflammatory pathways, such as *NF-κB* and *JAK/STAT*, along with epigenetic changes such as methylation of genes including *DAZAP2, CD55, and AIM2*, complicates the development of targeted therapies. In addition, many potential drugs, such as

TNF-α inhibitors or methylation-regulating agents, have significant systemic side effects that limit their widespread use. Therefore, the development of personalized therapies based on gene expression patterns, DNA methylation, and other genetic and epigenetic changes may offer more effective treatment options.

c. Stress pathways

Traumatic events can impair the regulation of the sympathetic adrenaline-medulla (SAM) and HPA axes, leading to abnormal circadian cortisol secretion rhythms. Cortisol, a key endocrine regulator in immune responses, plays a critical role in immune dysfunction. Chronic stress, such as that experienced by combat veterans, could cause resistance to the glucocorticoid receptor (*GCR*), resulting in chronic inflammation and increasing susceptibility to physical diseases and PTSD [48].

The *NR3C1* gene encodes the glucocorticoid receptor, which is essential for HPA axis function and cortisol regulation. Under normal conditions, high cortisol levels signal the brain to stop further cortisol production, maintaining homeostasis [60]. In PTSD, this feedback system might be compromised due to decreased expression or altered methylation of *NR3C1*, leading to prolonged or heightened stress hormone activity. This imbalance might exacerbate the persistent hyperactivation or hypoactivation of the HPA axis, both of which are linked to PTSD pathophysiology.

Given its role in cortisol regulation, *NR3C1* is a strong candidate for research on stress-related biomarkers [61]. Methylation patterns in *NR3C1* may enable early identification of PTSD risk or onset, particularly in trauma-exposed populations [62].

The *CREBZF* gene, involved in regulating the HPA axis, might exhibit increased methylation in its promoter regions, suppressing its expression and leading to increased stress sensitivity [63, 64]. Changes in stress response-related genes, such as glucocorticoid-regulating genes, *FKBP5*, have been documented in both cross-sectional and longitudinal investigations [27, 31]. Dysregulation of stress responses, linked to the *FKBP5* gene, influences PTSD risk and treatment responsiveness. Genetic and epigenetic alteration in FKBP5 contributes to PTSD pathophysiology, making it a potential therapeutic target or biomarker for monitoring treatment response [27].

d. Neuroplasticity and Neurodevelopment

Memory and fear play a central role in PTSD [65], as the condition is characterized by persistent traumatic memories and dysregulation of fear responses. Altered memory processing exacerbates the intrusive symptoms of PTSD, while hyperactive fear recall and impaired fear extinction contribute to hyperarousal and avoidance behaviors [66]. Disruptions in neurodevelopmental processes and synaptic plasticity hinder the brain's resilience and recovery after trauma, affecting neural connectivity and regulating fear and memory circuits. Disruptions contribute to the persistence of PTSD symptoms and may be linked to genetic and epigenetic changes in key neural circuits.

The *DYNC1H1, BDNF, and AKT1* genes, play crucial roles in axon guidance, hippocampal development, and neurogenesis [29, 32, 34]. The *DYNC1H1* gene regulates axonal transport, synaptic regeneration, and plasticity and its methylation can affect memory processes [64]. The *AP2B1* gene, involved in endocytosis, under the influence of methylation changes, may experience reduced neuronal transmission efficiency due to methylation changes [64, 67]. The *NR2E1* and *CREB1* genes are involved in fear response, while *BDNF* and *AKT1* regulate fear memory, and *CNR1* and *ETS-2* are associated with fear-related risk [25]. The *BDNF* gene methylation is related to neurogenesis and memory [3, 25, 28]. The *DSCAM* gene plays a significant role in neural development, contributing to dendritic patterning, self-avoidance, axon guidance, and synapse formation [68]. Downregulation of *DSCAM* in PTSD may impair neural network integrity and plasticity, leading to neurotransmitter release, cognitive deficits, and emotional dysregulations [3, 69]. *BDNF*, a protein, activates the phospholipase C -gamma, PI3K, and MAPK/ERK pathways, which are crucial for neurogenesis and synaptic plasticity [70]. Downregulation of these pathways correlated with reduced resilience and impaired recovery in PTSD, potentially leading to cognitive impairment.

LRP8 (ApoER2) is crucial for lysosomal breakdown and signal transmission. Its upregulation has been linked to cognitive decline, anxiety, disrupted nest construction, disturbed circadian rhythms, and altered stress responses in PTSD, suggesting its role in maladaptive neuronal development under chronic stress [71, 72]. *ATP6AP1L*, which facilitates lysosomal function and cellular energy production, may influence energy-dependent neural processes [73]. Deficiency in *ATP6AP1* results in immunodeficiency, hepatopathy, and cognitive impairment [74]. Downregulation of *ATP6AP1L* may disrupt energy-dependent neural processes and increase susceptibility to PTSD due to its involvement in the glucocorticoid receptor pathway and neural responses to stress[3].

The *CNR1* and *BDNF* genes are involved in dopamine and serotonin signaling, while *CREB1* and *HES4* genes are implicated in the cortisol hormone network [29]. *CYP2C8*, a key enzyme in the metabolism of neuroactive steroids and stress-regulating compounds [75], is involved in individuals with PTSD, potentially hindering the synthesis of neurosteroids that regulate anxiety and fear response [20].

These networks and genes represent epigenetic changes that can serve as biomarkers for improved

diagnosis and targeted treatment of PTSD. For example, *BDNF* plays a role in the pathogenesis of PTSD through various pathways and represents a potential therapeutic target. In the reviewed studies, Crombach *et al.,* [22] and Voisey *et al.,* [37] highlighted the therapeutic potential of interventions targeting epigenetic markers such as *BDNF* methylation. Voisey *et al*., [37] underscored the role of exercise and lifestyle interventions in reducing BNDF methylation and improving neural plasticity, offering a non-invasive treatment option. Hammamieh *et al.,* [25] and Wolf *et al.,* [39] advocated for integrating genetic and epigenetic markers into personalized treatment plans, leveraging tools such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and other gene-editing tools to modulate key pathways.

Studies indicated that miRNAs that target genes such as *DYNC1H1, BDNF*, and *GOLM1* are emerging as promising biomarkers for therapeutic monitoring and early diagnosis in cancer research [76-78]. These miRNAs may also prove valuable for the diagnosis and treatment of PTSD. Assessments of pathways at the protein level, such as the BDNF-PI3K-MAPK/ERK pathway, could serve as useful instruments for monitoring the development of PTSD progression [79].

Although this study provided valuable insights, several limitations must be acknowledged. First, much of the research focused on war veterans, which might limit the generalizability of the findings to other traumatized populations, such as civilians or children. Additionally, the use of different tissue sources, such as blood and saliva, might yield different results due to tissue-specific methylation patterns. Many studies focused on peripheral blood for methylation and gene expression analysis, but it remained unclear whether these findings apply to the brain or other relevant tissues.

Additionally, a large number of studies employed cross-sectional designs, making it difficult to track longitudinal epigenetic changes associated with PTSD or establish causal relationships.

Fully understanding gene-environment dynamics remains challenging due to insufficient research on the complex interplay between genetic predispositions, environmental factors, and trauma exposure. Furthermore, while promising biomarkers have been identified, their therapeutic significance is limited until confirmed in broader and more diverse populations. Methodological heterogeneity, including variations in tissue sources, analytical techniques, and control populations, further complicates direct comparisons between studies. This variability underscores the need for consistent methodologies in future research.

Gene expression and epigenetic changes, particularly DNA methylation, play a critical role in the pathophysiology of war-related PTSD. These alterations disrupt immune system pathways, inflammation, neuroplasticity, and stress-related mechanisms. Changes in neuroplasticity and memory-related gene expression, such as *BDNF, DSCAM,* and *CREB1*, could lead to impairments in learning processes, and fear extinction, along with cognitive and emotional symptoms characteristic of combat-related PTSD.

These findings highlighted the potential to target the immune and neurological pathways related to PTSD, enabling the design of more effective interventions and personalized treatments based on an individual's gene expression and epigenetic profile.

Future research should focus on validating these findings in larger and more diverse populations, exploring the intricate interplay of molecular pathways, and identifying novel biomarkers and therapeutic targets. These efforts will pave the way for developing more sensitive diagnostic tools and effective therapeutic interventions for PTSD, particularly its war-related subtype.

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