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Review

EPIGENETIC CONTRIBUTORS TO PTSD: A COMPREHENSIVE REVIEW

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SUMMARY

Background: *Post-traumatic stress disorder (PTSD) is a complex condition triggered by traumatic events. The molecular mechanisms underlying PTSD are not fully understood, but epigenetic modifications, particularly DNA methylation, may play a key role. The objective of this review was to identify the most significant epigenetic markers associated with PTSD.*

Materials and methods*: Our search yielded 325 articles, of which 19 met our inclusion criteria for detailed analysis: published between 2018 and 2024, original research, containing molecular-genetic and statistical data, reporting diagnostic verification methods, PTSD as a primary condition, and a sample of at least 40 patients*

Results: *the strongest correlation was found between PTSD and methylation changes in cg17057218, cg22324981, cg04755409 of BDNF, cg05656210, cg12169700, cg20756026 of MAD1L1, HLA-DPA1, HLA-DPB1 (chr6: 33047185 – 33049505) and SPATC1L (chr21: 47604052 – 47605174). The most works on associations of genetic clock with PTSD found significantly increased GrimAge acceleration in patients with PTSD.*

Conclusions: *Epigenetic modifications, particularly DNA methylation, play a significant role in PTSD pathophysiology. While specific gene methylation changes are associated with PTSD, the link between PTSD and epigenetic aging remains unclear. Variability across studies suggests that trauma type, duration, and genetic factors may influence these epigenetic processes. Further research is essential to fully understand these relationships.*

Key words: *epigenetics – GrimAge – CpG - methylation - post-traumatic stress disorder*

Abbreviations: *CpG – regions of DNA where a cytosine nucleotide is followed by a guanine nucleotide in the linear sequence of bases along its 5' → 3' direction; DNA - age acceleration; DNAm - methylation age acceleration; PTSD – Post-traumatic stress disorder*

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INTRODUCTION

Post-traumatic stress disorder (PTSD), historically referred to as battle fatigue syndrome or shell shock, is a severe mental health condition typically triggered by exposure to frightening or traumatic events where an individual experiences significant physical or psychological harm or threat. PTSD results from the prolonged exposure to traumatic conditions, leading to persistent feelings of helplessness, intense fear, and horror. Various events can precipitate PTSD, including physical, mental, or sexual assault at home or in the workplace, the unexpected death of a loved one, accidents, war, or natural disasters (Thakur et al. 2022).

The World Health Organization estimates a global PTSD prevalence of approximately 3.6%, with some studies indicating a significantly higher incidence of 8% among women (Kessler et al. 2017). Currently, the relevance of PTSD on the Post-Soviet territory has significantly increased due to the escalation of military conflicts.

Our evolving understanding of PTSD underscores that its development, like many other mental disorders, is significantly influenced by the interplay between environmental factors and genetic predisposition. The field of epigenetics bridges both sides of this debate, focusing on changes in gene expression that may be caused by environmental influences.

DNA methylation, mediated by DNA methyltransferases, typically decreases or silences gene transcription and occurs most frequently at the cytosine of a CpG site (a DNA sequence where cytosine is adjacent to guanine, separated by a phosphate). DNA methylation can also occur at non-CpG sites, including adenine bases, particularly in CpA and CpC sites. Differentially methylated regions (DMRs) are genomic regions exhibiting varying degrees of methylation across different samples, such as cells, tissues, or subjects (Blacker et al. 2019).

The epigenome can adapt to environmental influences through chemical and protein modifications of chromatin, which can be long-lasting and impact gene regulation and expression. An exciting area of recent research is epigenetic inheritance, which explores whether environmentally induced epigenetic changes can be transmitted to subsequent generations through the germline (Dias et al. 2015, Sweatt et al. 2013). The study of epigenetic mechanisms that arise from traumatic experiences forms a significant part of this rapidly expanding field. Numerous human-based epigenetic studies on PTSD have been conducted, with many focusing on candidate genes chosen based on animal models or genetic association findings, such as NR3C1, FKBP5, SLC6A3, and BDNF. For instance, BDNF is associated with memory, stress, and neuropsychiatric disorders.

A distinct group of studies focuses on "epigenetic clocks" - indicators used to assess the rate of cellular and tissue aging. Accelerated cellular aging is often considered a correlate of traumatic experiences and a significant risk factor for premature mortality. About 25% of CpG dinucleotides related to epigenetic clocks are located in genomic regions associated with the regulation of glucocorticoid receptors, which have been found to differ based on the experience of psychological trauma. Zannas et al. (2015) noted that the predictor of accelerated epigenetic aging is more likely to be lifelong accumulated stress rather than early childhood abuse or recent acute traumatic events. Multiple studies using Hannum's epigenetic clock have shown that individuals with PTSD have higher DNA methylation age values compared to their chronological age. In contrast, studies using Horvath's epigenetic clock reported a negative association between DNAm age acceleration and PTSD and the development of PTSD symptoms. The most recent epigenetic clock, DNAm GrimAge, is a better predictor of age-related health outcomes, compared to earlier clocks, as it has been specifically trained on time-to-death and age-related biochemical markers and smoking packs per year. Recent evidence demonstrates a significant association between PTSD and GrimAge acceleration. Recent studies also suggest that epigenetic marks might be transmitted to the next generation, influencing the risk of diseases in offspring. However, these studies have typically been small or underpowered and require expansion and replication.

The objective of this review was to identify the most significant epigenetic markers associated with PTSD.

SUBJECTS AND METHODS

To determine the optimal literature search procedure for our review, we conducted the search in two steps: we first sought to identify the appropriate genes and CpGs, and then undertook a detailed analysis of the candidate genes in PTSD, using PubMed as a primary database. We carried out the first step of our search using the following search queries: «PTSD epigenetic markers», «PTSD epigenetics», and conducted the second step with search queries for individual genes that emerged from step 1: «PTSD methylation», «PTSD GrimAge».

The search yielded 325 articles, of which 19 met our inclusion criteria for detailed analysis: published between 2018 and 2024, original research, containing molecular-genetic and statistical data, reporting diagnostic verification methods, PTSD as a primary condition, and a sample of at least 40 patients.

RESULTS

DNA Methylation

Yang et al. (2021) investigated the relationship between methylation changes in FKBP5 and PTSD symptom severity among 96 participants. They identified 3,113 probes where changes in methylation levels were significantly associated with changes in symptom severity ($p<0.01$). The majority of these associations were positive (2,072), meaning that reduced methylation corresponded with decreased PTSD symptom severity. Specific CpG sites within FKBP5, such as cg14284211 (chr6: 35570224 near exon 1) and cg03591753 (chr6: 35659141 near exon), showed less methylation with decreasing symptom severity. Additionally, 3.7% of the 3,113 differentially methylated probes were also significantly associated ($p<0.01$) with cell composition, age, or gender.

Carvalho et al. (2023) investigated the relationship between methylation at three CpG sites (CpG1 at position 328, CpG2 at position 321, and CpG3 at position 318) in a sample of 64 women with PTSD, some of which experienced child sexual abuse (CSA). They found a negative association between CpG2 methylation and hyperarousal symptoms in the PTSDCSA+ group (adjusted $p=0.003$) compared to the PTSDCSA- group ($p>0.05$). No significant associations were observed between other PTSD symptoms and methylation at the other CpG sites (CpG1 and CpG3).

Guo et al. (2018) examined methylation levels in the promoter region of the BDNF gene in a cohort of 322 PTSD patients and 215 control subjects. They found no significant differences in methylation levels at CpG8, CpG10, and CpG11 of BDNF between the control and PTSD groups ($p>0.05$). However, significant differences were observed at CpG1, CpG2, CpG3, CpG4, CpG5, CpG6, CpG7, CpG9, CpG12, CpG13, CpG15, CpG16, CpG17, and CpG18 ($p<0.05$). Methylation levels of CpG1 and CpG18 were significantly associated with aggressive violent trauma, while CpG7 methylation was correlated with traffic accident trauma (Table 1).

Table 1. Epigenetic findings associated with PTSD

Reference	Cohort (gender, race, groups, causes)	Gene(s)	Key findings
Occean et al. (2022)	Both female and male; Black, White, Other; Lifetime PTSD(+) (n = 97; 52.7 ± 12.6 years); PTSD(-) (n = 76; 55.0 ± 15.1 years) Assaultive violence, Other injury or shocking experience, Learning about traumas to a loved one, Unexpected death of a close friend or relative	NFATC1	PTSD(+): cg17057218 (F=16.27, p <0.001, FDR=0.014), cg22324981 (F=12.57, p <0.001, FDR=0.029), cg04755409 (F=12.44, p <0.001, FDR=0.029).
Piccinini et al. (2023)	Only female; Women PTSD(+) (n = 40); Women with at least one diagnostic criterion (n=73) Trauma-exposed (n = 62) Non trauma-exposed (n = 50) Sexual violence, physical violence	BDNF, DRD2, FKBP5, IGF2	PTSD(+): BDNF (p<0.01), DRD2 (p<0.01), FKBP5 (p<0.05), IGF2(p<0.01).
Guo et al. (2018)	Both female and male; Asian (Han predominantly); PTSD(+) (n=322; 39.25±7.16 years); PTSD(-) (n=215; 38.68±7.02 years)	BDNF	PTSD(+): CpG1-CpG7, CpG9, CpG12, CpG13, CpG15-CpG18 (p<0.05).
Snijders et al. (2020)	Only male; European, African, Other; Military veterans PTSD(+) (n = 123); PTSD(-) (n=143)	MAD1L1	PTSD(+): cg05656210 (p<0.001), cg12169700, cg20756026 (p<0.05).
Hummel et al. (2022)	Only female; 60 people (20-65 years)	NR3C1, FKBP5, SLC6A4, OXTR, ADORA1, TSPAN9, RPS6KA2, DMR-1	PTSD(+): no statistically significant differences (p>0.05) were found in NR3C1, FKBP5, SLC6A4, OXTR, ADORA1, TSPAN9, RPS6KA2, DMR-1.
Logue et al. (2020)	Both female and male; Military veterans PTSD(+) n=378; PTSD(-) n=135	G0S2	PTSD(+): cg19534438 (p<0.05).
Tudor et al. (2022)	Only male; Military veterans 555 people (48-62 years) - 258 PTSD cases	HNF1A	PTSD(+): no statistically significant differences were found in HNF1A.
Conrad et al. (2018)	Both female and male; Survivors of the war, military veterans; Ugandan cohort: total (n = 924; 31.26±10.74 years), PTSD(+) group (n = 644; 69.70%) Rwandan cohort: total (n = 371; 34.65±5.88 years), PTSD(+) group (n = 263; 70.89%)	NOTCH3	PTSD(+): no statistically significant differences were found in NOTCH3 methylation.
Cosentino et al. (2023)	Both female and male; Civilians PTSD(+) (n = 37); Traumatized PTSD(-) (n=48); Non-traumatized PTSD(-) (n = 47)	MECP2	PTSD(+): Reduced MECP2 expression associated with severe PTSD symptoms (R^2 = 7.4%; β = 0.27, p<0.05).
Katrinli et al. (2021)	Both female and male; African Americans; PTSD(+) (n = 187; 41.58±11.45 years); PTSD(-) (n = 367; 42.04±12.86 years)	HLA-DPA1, HLA-DPB1, SPATC1L	PTSD(+): hypermethylation of HLA-DPA1, HLA-DPB1 (chr6: 33047185 – 33049505) and SPATC1L (chr21: 47604052 – 47605174) (p<0.001).
Hossack et al. (2020)	Both female and male; Caucasian, African American, Hispanic/Latino, Asian, Other; Military veterans; PTSD(+) (n = 70; mean age 38.7 years); PTSD(-) (n = 100; mean age 35.1 years)	BDNF, NR3C1, MAN2C1, SKA2, TLR8, SLC6A4, IL-18	PTSD(+): hypomethylation of all CpG of BDNF and NR3C1 sites (p<0.05); hypomethylation of MAN2C1 CpG (p<0.01), this finding persisted after controlling for antidepressant use. Changes in SKA2, TLR8, SLC6A4, IL-18 methilation were not associated with PTSD.
Kang et al. (2019)	Only male; Military veterans; PTSD(+) (n = 123; 63.11±3.54 years) PTSD(-) (n = 116; 62.66±4.19 years)	FKBP5	PTSD(+): hypomethylation of T allele rs1360780 of FKBP5 (p<0.05).

Logue et al. (2020) identified a significant association between PTSD and the methylation site cg19534438 in the G0S2 gene ($p=1.19\times10^{-7}$, adjusted p=0.048) in a cohort consisting of 378 Veterans with lifetime PTSD and 135 controls. This finding was replicated in an independent meta-analysis by the PGC-PTSD-EWAS consortium involving military cohorts (p=0.0024). Additionally, an association was observed with the smoking-related locus cg05575921 in AHRR, despite controlling for a methylation-based smoking score ($p=9.16\times10^{-6}$).

Conrad et al. (2020) investigated genomic methylation of saliva-derived DNA and its association with lifetime PTSD risk in cohorts from Northern Uganda (n=924) and Rwanda (n=371). They examined whether NOTCH-related gene sets were enriched for PTSD associations. Significant associations were found with the SNP rs2074621 (NOTCH3) (p uncorrected = 0.04) in both cohorts and with methylation at CpG site cg17519949 (NOTCH3) (p uncorrected = 0.05) in the Rwandan cohort. However, these epigenetic associations did not survive multiple testing correction. The other findings are presented in Table 1.

GrimAge

Verhoeven et al. (2018) discovered a negative relationship between telomerase activity and Δage in the PTSD positive group (β=-0.35; p=0.007). This study analyzed the associations between estimated epigenetic age and various factors in a sample of 160 male combat-exposed war veterans, including 79 with PTSD and 81 without PTSD. They concluded that veterans with PTSD exhibited significantly lower epigenetic age profiles compared to their non-PTSD counterparts (PTSD positive Δage = 3.3, PTSD negative Δage = 4.0).

Katrinli et al. (2023) observed increased DNA methylation GrimAge acceleration in PTSD patients compared to a combined control group (trauma-exposed and non-trauma exposed) ($p = 8.8 \times 10^{-9}$), indicating a higher risk of mortality in those with PTSD. The study included 140 US military veterans who fought in Iraq and/or Afghanistan, comprising 112 current PTSD cases enrolled in a PTSD treatment study, 28 veterans without a history of PTSD, and 59 non-trauma exposed controls at baseline and post-treatment (24 weeks after baseline).

Katrinli et al. (2020) reported that lifetime trauma burden (p=0.03), current PTSD (p=0.02), and lifetime PTSD (p=0.005) were associated with GrimAge acceleration, suggesting a shorter predicted lifespan. The association with lifetime PTSD was replicated in an independent cohort (p=0.04).

Wang et al. (2022) found that twins with current PTSD exhibited significantly advanced DNAm age acceleration compared to twins without PTSD for five out of six measures of DNAm age acceleration. The study identified an association between PTSD and acceleration in DNAm surrogates of tissue inhibitor metalloproteinase-1 (TIMP-1), β-2 microglobulin (B2M), and growth differentiating factor-15 (GDF-15). Additionally, greater severity of trauma-related detachment (feeling distant or cut off from others) (OR = 1.73, 95% CI = 1.22–2.45, p = 0.002) and sleep disturbance (OR = 1.51, 95% CI = 1.16–1.95, p = 0.002) were independently associated with accelerated GrimAge. The study involved 296 male twins from the Vietnam Era Twin Registry (Table 2).

Table 2. Findings in GrimAge acceleration related to PTSD

Reference	Cohort (gender, race, groups, causes)	Key findings
Verhoeven et al. (2018)	Only male; Hispanic, Non-hispanic black, Non-hispanic white, Asian, Other; Military veterans; PTSD(+) (n=79; 33.0±7.8 years) PTSD(-) (n=81; 32.6±8.0 years)	PTSD(+): lower epigenetic age (p<0.05) (PTSD positive Δage = 3.3, PTSD negative Δage = 4.0).
Katrinli et al. (2023)	Both female and male; White, Black, Other; Military veterans; PTSD(+) (n=112; 33.0±7.8 years) Combat controls (n=28; 33.75±8.23 years); Non-combat controls (n=59; 26.39±7.76 years)	PTSD(+): Increased GrimAge acceleration (p<0.001).
Katrinli et al. (2020)	Both female and male; African Americans; Current PTSD(+) (n=218; 40.93±11.43 years); Lifetime PTSD(+) (n=209; 43.30±11.80 years); PTSD(-) (n=427; 42.80±12.70 years); Lifetime and childhood trauma	Increased GrimAge acceleration in current PTSD(+) (p<0.05) and Lifetime PTSD(+) (p<0.01) groups.
Wang et al. (2022)	Only male; Military veterans; PTSD(+) (n=24; 57.4±2.2 years) PTSD(-) (n=272; 56.0±3.4 years)	PTSD(+): increased simple DNA methylation age acceleration (AA) based on Horvath's epigenetic clock (Horvath's AA), Intrinsic Epigenetic AA, Extrinsic Epigenetic AA and DNA methylation AA based on Pheno age (p<0.05).

DISCUSSION

Methylation changes in the promoter regions of the BDNF gene have been widely linked to variations in BDNF levels within the prefrontal cortex, with PTSD patients typically exhibiting decreased BDNF levels. This reduced methylation may correspond to increased BDNF protein levels in the hippocampus and amygdala, which could contribute to pathological fear memory extinction and the consolidation of traumatic memories (Redlich et al. 2020, Moser et al. 2015).

Supporting this, Hossack's (2020) study reports that hypomethylation across all CpG sites of BDNF is prevalent among PTSD patients, a finding echoed in Guo's (2018) research, which identified hypomethylation at specific CpG sites (CpG1, CpG2, CpG3, CpG4, CpG5, CpG6, CpG7, CpG9, CpG12, CpG13, CpG15, CpG16, CpG17, and CpG18) in the BDNF promoter region.

Research on animal models, particularly rats, has shown that physical exercise induces hypomethylation in the BDNF promoter, leading to increased gene expression (Oliff et al. 1998). Piccinini's (2023) findings further validate this connection, demonstrating that hypermethylation of BDNF is associated with stress, as similar results were observed in veterans diagnosed with PTSD. Additionally, significant associations were found between stress and methylation changes in the DRD2 and IGF2 genes.

IGF2, a gene regulated by genomic imprinting, encodes insulin-like growth factor 2, a key regulator of fetal and placental growth. IGF2 also plays crucial roles in several brain functions, including memory and mood regulation, and its dysfunction may be linked to conditions such as autism. Evidence also suggests that BDNF expression is critical in response to IGF2 stimulation, indicating a functional relationship between BDNF and DRD2 (Piccinini et al. 2023).

Given the known role of NOTCH signaling in learning, memory, and fear responses, it is plausible that NOTCH genes are involved in PTSD development as well. Indeed, Conrad et al. (2020) identified a significant association between lifetime PTSD risk and methylation at the CpG site cg17519949 in the NOTCH3 gene ($p=0.05$).

Common variants in the FKBP5 gene have been linked to increased FKBP5 protein expression, which can result in glucocorticoid receptor resistance and impaired negative feedback within the HPA axis. This disruption leads to a slower return to baseline cortisol levels following stress, potentially elevating the risk of developing PTSD symptoms (Bremner & Pearce 2016, Passos et al. 2015, Ridker & Lüscher 2014). Conversely, lower methylation in the body region of FKBP5 may result in reduced gene and protein expression, which could decrease the risk of PTSD symptoms. Yang et al. (2021) highlight the association between hypomethylation of FKBP5 exons and PTSD genesis, particularly at CpG sites cg14284211 (chr6: 35570224) near exon 1 and cg03591753 (chr6: 35659141) near another exon of FKBP5. This link between FKBP5 hypomethylation and PTSD development is further supported by Piccinini et al. (2023). Additionally, Kang et al. (2019) propose the role of the T-allele of rs1360780, which may be associated with FKBP5 hypomethylation and subsequent PTSD risk. However, Hummel et al. (2022) argue that FKBP5 may not play a significant role in the pathogenesis of PTSD, suggesting the need for further research to clarify its involvement.

The NFATC1 gene, which encodes a calmodulin-dependent isoform of the NFAT transcription factor family, is involved in various physiological processes. This suggests that NFATC1 could modulate stress responses, thereby contributing to the development of stress-related psychopathologies, including PTSD. Occean et al. (2022) confirmed the hypothesis that methylation of certain CpG sites within the NFATC1 gene is associated with lifetime PTSD, strengthening the evidence for its role in the disorder.

Similarly, SKA2 (spindle and kinetochore-associated protein 2) plays a crucial role in cellular mitosis and glucocorticoid activity. Unchanged or decreased methylation of SKA2 may indicate a persistent high cortisol stress response, which could lead to HPA axis exhaustion and, subsequently, PTSD development. Hossack et al. (2020) found a significant association between the A/A genotype (rs7208505) and SKA2 hypomethylation, which was linked to the development of PTSD, suggesting that this genetic and epigenetic interplay may be crucial in understanding the disorder's etiology.

NR3C1 encodes the glucocorticoid receptor, which binds glucocorticoids and plays a critical role in regulating the HPA axis. Considering the SKA2 gene's function as a chaperone for the glucocorticoid receptor, it is not surprising that both genes exhibit similar methylation patterns. Research by Guo (2018) and Hossack (2020) emphasizes the significant contribution of NR3C1 methylation to the development of PTSD ($p\leq0.004$). However, as with other candidate genes, some studies question the influence of NR3C1 methylation on PTSD, as discussed in Hummel et al. (2022).

In a longitudinal study by Snijders et al. (2020), PTSD was linked to decreased methylation in HLA-DPB1 DMR, which comprises a combination of different SNPs (haplotypes) resulting in functionally distinct proteins. Further supporting this, Katrinli et al. (2021) identified hypermethylation in two regions associated with PTSD after correcting for multiple tests: one in the gene body of HLA-DPB1 ($p=2.89\times10^{5}$) and the other in the promoter region of SPATC1L ($p=0.001$).

HNF1A encodes a transcription factor that regulates the expression of numerous genes involved in various metabolic and immunological processes. Tudor et al. (2022) found that hypermethylation at the CpG3 site of HNF1A was associated with PTSD, further highlighting the gene's potential role in the disorder.

MECP2 serves as a scaffold protein, recruiting chromatin remodeling complexes and DNA methyltransferases to methylated DNA loci. This makes it a strong candidate for mediating post-trauma epigenetic rearrangements. Cosentino et al. (2023) found that MECP2 expression is directly associated with higher Adverse Childhood Experiences (ACE) scores ($p=0.015$), suggesting that early life stress might contribute to PTSD risk through epigenetic modifications of this gene.

The G0S2 protein plays a crucial role in regulating lipid metabolism, acting as a negative regulator of lipolysis. Logue et al. (2020) identified a significant association between hypermethylation of the cg19534438 site within the G0S2 gene and PTSD ($p=1.19\times10^{-7}$, adjusted $p=0.048$), suggesting that alterations in lipid metabolism may contribute to the pathophysiology of PTSD.

MAD1L1 is integral to the mitotic spindle-assembly checkpoint (SAC), which ensures proper chromosome attachment to the microtubule spindle and correct chromosome segregation. In the PTSD GWAS conducted by the Million Veteran Program (MVP), carriers of the minor allele of rs11761270 were found to have decreased methylation levels and an increased risk of developing PTSD (Snijders et al. 2020). These findings align with Snijders et al. (2020), where PTSD cases exhibited a reduction in methylation from pre- to post-deployment. Such results indicate that specific methylation profiles within MAD1L1 may not only be risk factors for PTSD but also for other psychiatric disorders (Levey et al. 2020).

Additionally, there is growing evidence that the methylation of repetitive elements, such as long interspersed nuclear element 1 (LINE-1), could be linked to the development of psychiatric conditions. Carvalho et al. (2023) found a negative association between CpG2 methylation and hyperarousal symptoms in individuals with PTSD, although no significant associations were observed between other PTSD symptoms and other CpG sites.

Epigenetic clocks

Several studies have identified a link between GrimAge acceleration - a measure of biological aging - and the presence of PTSD (Verhoeven et al. 2022). For instance, Katrinli et al. (2023) found significant associations between GrimAge acceleration and PTSD at baseline, as well as with premature mortality. Their findings indicated that GrimAge acceleration was positively correlated with estimated neutrophil proportions and negatively correlated with T and B lymphocyte proportions. These shifts in immune cell proportions suggest an inflammatory response and immune dysfunction, which are also linked to increased mortality risk. This aligns with earlier research showing a positive correlation between GrimAge acceleration and CD8+ CD28− T cell proportions, a marker of immunesenescence, highlighting the immune system's role in epigenetic aging.

In contrast, Wang et al. (2022) conducted a study comparing the epigenetic age of twin pairs, where one twin had PTSD. Their results indicated an association between accelerated DNA methylation age (DNAm age) and PTSD; however, no such relationship was found between GrimAge and PTSD. This suggests that different epigenetic clocks may capture distinct aspects of biological aging in relation to PTSD.

Interestingly, Verhoeven et al. (2022) examined epigenetic age acceleration in male combat-exposed war veterans and reported unexpected findings. Contrary to what might be anticipated, veterans with PTSD exhibited less accelerated epigenetic aging compared to those without PTSD.

These conflicting results underscore the complexity of the relationship between PTSD and epigenetic aging. The field remains underexplored, and further research is essential to draw more definitive conclusions regarding the impact of PTSD on biological aging.

CONCLUSION

The findings discussed highlight the intricate and multifaceted relationship between PTSD and epigenetic modifications. Our analysis underscores the importance of several candidate genes, including FKBP5, NR3C1, G0S2, MAD1L1, HLA-DPB1, HNF1A, and MECP2, in the pathogenesis of PTSD. These genes are implicated in crucial biological processes such as glucocorticoid receptor signaling, immune response, and cellular stress mechanisms, all of which are relevant to the development and maintenance of PTSD symptoms.

Additionally, the exploration of epigenetic clocks, particularly GrimAge, reveals significant associations between accelerated biological aging and PTSD. However, the evidence remains conflicting, as demonstrated by Verhoeven et al. (2022), who reported less accelerated epigenetic aging in PTSD-affected individuals - a finding that challenges previous assumptions and highlights the complexity of epigenetic aging in PTSD.

The discrepancies in results across studies suggest that the relationship between PTSD and epigenetic changes is not straightforward and may be influenced

by a variety of factors, including the specific epigenetic clock used, the genetic background of the individuals studied, and the type of trauma exposure. These findings call for further research to clarify the mechanisms by which epigenetic modifications contribute to PTSD and to explore the potential of these modifications as biomarkers for diagnosis and targets for therapeutic interventions.

In conclusion, while significant progress has been made in understanding the epigenetic underpinnings of PTSD, much remains to be learned. The variability in findings highlights the need for more comprehensive studies with larger sample sizes and the inclusion of diverse populations. Such efforts will be crucial in elucidating the complex interplay between genetic predispositions, environmental stressors, and epigenetic changes in the context of PTSD, ultimately leading to more effective strategies for prevention, diagnosis, and treatment.

Limitations

The study is subject to the typical limitations of a review work. The present results are qualified by the heterogeneous study designs of the analyzed studies, and inadequate sample size for drawing general conclusions. We see a need for further research related to the precise PTSD contributors, taking into account polygenic nature and epigenetic mechanisms of the disease.

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Contribution of individual authors:

Alexey Sustretov, Alexey Kuznetsov, Daniil Kokorev & Arseny Gayduk: have composed the primary idea and specified the hypothesis.

Olga Pesneva & Alexander Kolsanov: have been responsible for data collection.

Timur Syunyakov: conducted an analysis of dana.

Alexey Kuznetsov have been responsible for the literature data collection and wrote the first draft of the manuscript.

Timur Syunyakov & Arseny Gayduk: managed the detailed manuscript editing and revision, preparation of the manuscript.

All auhors gave their final approval of the manuscript for submission.

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