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Citation

Smith, A. K., Katrinli, S., Maihofer, A. X., Aiello, A. E., Baker, D. G., Boks, M. P., ... Zannas, A. S. (2025). Cell-type-specific and inflammatory DNA methylation patterns associated with PTSD. *Brain, Behavior, And Immunity*, *128*, 540-548. doi:10.1016/j.bbi.2025.04.031

Brain, Behavior, and Immunity 128 (2025) 540–548

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

Cell-type-specific and inflammatory DNA methylation patterns associated with PTSD

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https://doi.org/10.1016/j.bbi.2025.04.031
Received 6 December 2024; Received in revised form 11 April 2025; Accepted 21 April 2025

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ARTICLE INFO

Keywords:
PTSD
Trauma
Inflammation
CRP
B-cells
Immune
EWAS
DNA methylation

ABSTRACT

Background: Epigenetic modifications, including DNA methylation (DNAm), can change in response to traumatic stress exposure, and may help to distinguish between individuals with and without PTSD. Here, we examine the DNAm patterns specific to immune cell types and inflammation in those with PTSD.

Methods: This study includes 3,277 participants from 11 cohorts participating in the Psychiatric Genomics Consortium (PGC) PTSD Epigenetics Workgroup. DNAm was assayed from blood with the MethylationEPIC BeadChip. A standardized QC pipeline was applied and used to impute cell composition. Within each cohort, we identified cell-type-specific DNAm patterns associated with PTSD, controlling for sex (if applicable), age, and ancestry. Meta-analyses were performed from summary statistics.

Results: PTSD cases had lower proportions of B cells and NK cells as well as higher proportions of neutrophils when compared to trauma-exposed controls. Overall, we identified 96 PTSD-associated CpGs across six types of immune cells. Most of these differences were identified in B cells, with 95 % exhibiting lower methylation levels in those with PTSD. Interestingly, the PTSD-associated CpGs annotated to a gene in B cells were enriched in a recent GWAS of PTSD ($p < 0.0001$).

Conclusions: This study identifies novel PTSD-associated CpGs in individual immune cell types and supports the role of immune dysregulation and inflammation in PTSD.

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1. Introduction

DNA methylation (DNAm) is a key epigenetic mechanism through which gene expression is regulated in response to environmental changes. Multiple studies have demonstrated that DNAm at specific CpG sites (CpGs) changes in response to traumatic stress exposure (Katrinli et al., 2022a; Logue et al., 2020; Smith et al., 2020; Snijders et al., 2020; Uddin et al., 2018), suggesting that DNAm may be one mechanism through which the body responds to trauma. Indeed, many epigenome-wide association studies (EWAS) conducted in blood and in the brain report robust associations between DNAm and PTSD (Katrinli et al., 2022a; Logue et al., 2020; Smith et al., 2020; Snijders et al., 2020; Uddin et al., 2018) although methodological questions remain.

PTSD diagnosis requires exposure to traumatic event(s), and individuals with higher levels of trauma exposure are at higher risk of developing PTSD (Kessler et al., 2005; Kessler et al., 1995). The biological sequelae of PTSD are systemic, and recently published reviews detail PTSD-associated differences in the nervous system, cardiometabolic systems, metabolic systems, and the immune system (Katrinli et al., 2022b; Ke et al., 2023; Li et al., 2024; Lushchak et al., 2023; Shalev et al., 2024; Sumner et al., 2023; Tian et al., 2023). Because DNAm is cell-type-specific, PTSD-associated differences identified in brain-derived cells and blood-derived cells may represent different aspects of PTSD pathogenesis and/or sequelae. While many studies have noted correlated DNAm patterns in different tissues or cross-tissue associations in PTSD and other disorders (Davies et al., 2012; Katrinli et al., 2024; Logue et al., 2020; Nunez-Rios et al., 2022; Smith et al., 2015; Tylee et al., 2013), the majority of EWAS examining psychiatric disorders are conducted in blood, in which the nucleated elements are a heterogeneous mixture of immune cell types.

There is a renewed recognition of the role of the immune system and systemic inflammatory factors in PTSD and other psychiatric disorders (Friend et al., 2022; Katrinli et al., 2022b). Multiple studies reported differences in the immune cell composition of blood from those with

PTSD when compared to trauma-exposed controls (Aiello et al., 2016; Passos et al., 2015; Yang and Jiang, 2020). Hence, studies examining DNAm differences associated with PTSD control for cell composition (Katrinli et al., 2022a; Logue et al., 2020; Smith et al., 2020; Snijders et al., 2020; Uddin et al., 2018). Several methods leverage the distinct DNAm patterns that define an individual cell type to estimate cell composition in DNA derived from a heterogenous source, such as whole blood (Houseman et al., 2012; Salas et al., 2018; Zhu et al., 2022). Controlling for differences in cell composition, which can vary between individuals and longitudinally within individuals, reduces the risk of false positives. However, as the differences in cell composition may also result from the biological processes underlying a disorder, this strategy may miss cell-type-specific associations, particularly when they occur in less abundant cell types.

While some studies have purified and subsequently measured DNAm across specific blood cell types (Liu et al., 2013; Reynolds et al., 2017), the cost and effort of this approach make it impractical for large sample sizes, which are essential for identifying robust associations with complex phenotypes such as PTSD. Fortunately, recent advancements have led to the development of computational methods that enable deconvolution of bulk-level DNAm data into cell-type-specific DNAm signals without the need for cell sorting (Li et al., 2019; Rahmani et al., 2019; Wang et al., 2021; Zheng et al., 2018). Such computational deconvolution opens exciting opportunities to leverage the bulk DNAm datasets that are already available in large cohorts to gain cell-type-level biological insights. The power of this approach was recently demonstrated by Hettema and colleagues, who identified DNAm differences in monocytes and granulocytes that associated with a lifetime history of anxiety disorders, with the cell-type-specific analysis identifying more associations than the cell-type-corrected analysis of whole blood (Hettema et al., 2023).

Understanding the immune system response following traumatic stress exposure and in those with PTSD is integral to our understanding of the disease process and its many comorbidities. This study will be the first to explore cell-type-specific associations across a large number of studies of trauma-exposed subjects who developed PTSD and unaffected controls. Here, we leverage DNAm data from the Psychiatric Genomic Consortium (PGC) PTSD Epigenetics Workgroup to conduct the largest evaluation of immune cell composition in PTSD to date. We then identify cell-type-specific DNA methylation patterns that associate with PTSD. Finally, we examine the role of inflammation in PTSD in relation to immune cell composition and PTSD-associated CpGs.

2. Methods

2.1. PTSD cohorts and Assessments

The study includes 3,277 participants from 11 cohorts (Table 1) with further description of the individual cohorts provided in the Supplemental Methods. The PTSD diagnosis at the time of the blood draw was assessed by each cohort following the harmonization guidelines established by the PGC-PTSD Workgroup (Katrinli et al., 2024; Logue et al., 2015). If applicable for a cohort, participants with a prior history of PTSD who had recovered or were asymptomatic were excluded. All non-PTSD participants (i.e., controls) experienced at least one traumatic event. All participants provided informed consent, and all studies were approved by an institutional review board. Detailed cohort descriptions are provided in the Supplementary Methods.

2.2. DNA methylation assessment and quality control (QC)

Whole-blood DNAm was measured using the Illumina MethylationEPIC BeadChip. Studies applied a standardized quality control (QC) pipeline developed by the consortium (available at https://github.com/PGC-PTSD-EWAS/EPIC_QC). Following the removal of poorly performing samples (e.g., low call rates) and problematic (e.g., detection p-values > 0.01 or cross-hybridizing) probes, data was normalized using single-sample Noob (ssNoob) as implemented in *minfi* (Fortin et al., 2017*)*. *ComBat* was used to account for technical variation due to chip and position, while preserving signals related to PTSD, age, and sex (if applicable) (Leek et al., 2012). A DNAm-based smoking score was calculated as previously described (Logue et al., 2020). For each sample, the proportion of CD4 + T, CD8 + T, natural killer (NK), B cells, monocytes, and neutrophils was estimated using the Robust Partial Correlation (RPC) method in *Epidish* (Teschendorff et al., 2017) and the MethylationEPIC reference data (Salas et al., 2018).

Table 1
Overview of participating cohorts.

Cohort	N	Cases N (%)	Female N (%)	White N (%)	Black N (%)	Age mean (SD)
Army STARRS	216	106 (49 %)	0 (0 %)	149 (69 %)	22 (10 %)	25.13 (4.82)
AURORA	206	57 (28 %)	154 (75 %)	67 (33 %)	131 (64 %)	39.24 (14.17)
BEAR	162	36 (22 %)	119 (73 %)	112 (69 %)	3 (2 %)	15.16 (1.45)
DCHS	95	46 (48 %)	95 (100 %)	0 (0 %)	54 (57 %)	26.81 (5.2)
DNHS	423	26 (6 %)	255 (60 %)	23 (5 %)	384 (91 %)	54.54 (16.87)
GTP	479	158 (33 %)	340 (71 %)	12 (3 %)	448 (94 %)	42.22 (12.25)
MRS	127	64 (50 %)	0 (0 %)	88 (69 %)	5 (4 %)	23.07 (2.18)
NCPTSD/ TRACTS	1028	638 (62 %)	231 (22 %)	706 (69 %)	123 (12 %)	44.06 (13.7)
NIU	140	18 (13 %)	140 (100 %)	110 (79 %)	19 (14 %)	26.01 (1.74)
PRISMO	89	24 (27 %)	9 (10 %)	74 (83 %)	3 (3 %)	27.51 (8.63)
PROGrESS	140	112 (80 %)	14 (10 %)	89 (64 %)	40 (29 %)	34.77 (8.33)
TOTAL	**3277**	**1351 (41 %)**	**1452 (44 %)**	**1430 (44 %)**	**1357 (41 %)**	**36.9 (11.79)**

Participating cohorts: Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS), AURORA, Biomarkers, social, and affective predictors of suicidal thoughts and behaviors in adolescents (BEAR), Drakenstein Child Health Study (DCHS), Detroit Neighborhood Health Study (DNHS), Grady Trauma Project (GTP), Marine Resiliency Study (MRS), Boston VA National Center for PTSD (NCPTSD) and Translational Research Center for TBI and Stress Disorders (TRACTS), Northern Illinois University (NIU), Prospective Research in Stress-related Military Operations (PRISMO), PROlonGed ExpoSure and Sertraline Trial (PROGrESS).

2.3. Statistical analysis

2.3.1. Analyses of cell composition

Differences in cell composition between PTSD cases and trauma-exposed controls were examined using a multivariable regression that controlled for age, sex, smoking score, and cohort. The change in cell type proportions was also assessed in relation to change in posttraumatic stress symptoms in a subset of cohorts with longitudinal data available before and after military deployment (i.e. MRS, PRISMO, and Army STARRS cohorts). For this analysis, we regressed delta cell proportions on delta PTSD symptoms, adjusting for the time between pre- and post-deployment. We also examined the association between cell composition and C-reactive protein (CRP) levels in 1,077 participants from three cohorts (GTP, MRS, and NCPTSD/TRACTS). Because the scales of the continuous CRP values varied across cohorts, results from each cohort were combined using the weighted sum of z-scores (Stouffer's) method as implemented in the *metap* package. Briefly, p-values were converted into z-scores by taking direction of effects into account, and the square root of the sample sizes were used as weights.

To evaluate whether inflammation-associated DNAm patterns correlated with PTSD-associated DNAm patterns, we leveraged the summary statistics from publicly available *meta*-analyses conducted in whole blood. Pearson correlations were used to compare the effect sizes of 1,625 CRP-associated CpGs (Wielscher et al., 2022) to the effect sizes of PTSD-associated CpGs from the most recent PGC PTSD Epigenetics Workgroup *meta*-analysis (Katrinli et al., 2024).

2.3.2. Cell-type-specific methylation analyses

Within each cohort, DNAm was regressed on PTSD controlling for sex (if applicable), age, cell proportions, and ancestry. TOols for the Analysis of heterogeneouS Tissues (TOAST) (Li and Wu, 2019) was used to identify PTSD-associated CpGs in each of the leukocyte cell types (i.e., CD4 + T, CD8 + T, NK cells, B cells, monocytes, and neutrophils). Because PTSD was categorical and to maximize power, an inverse-variance weighting (IVW) *meta*-analysis was performed using *meta* (Balduzzi et al., 2019), and an epigenome-wide significance threshold of $p < 9.0e\text{-}8$ was applied across all analyses (Mansell et al., 2019). Gene Ontology (GO) enrichment analyses were conducted for the top 500 CpGs in each cell type using *missMethyl* (Phipson et al., 2016). An FDR threshold of 5 % was used to identify significant GO enrichment.

3. Results

3.0.1. Participating cohorts

Sample characteristics for the 11 cohorts that participated in this study are summarized in Table 1. All participants were trauma-exposed, with 41 % meeting the criteria for PTSD at the time of their blood draw. The individual cohorts vary in terms of sex and ancestry; overall, 44 % of the participants were female, and 41 % were of African ancestry. Univariate analysis revealed differences in cell type composition based on age, female sex, and smoking score (Table S1).

3.0.2. PTSD association with cell types and cell-type-specific DNA methylation

Cell type proportions were compared between PTSD cases and trauma-exposed controls. After controlling for age, sex, smoking score, and cohort, participants with PTSD were more likely to have lower proportions of B cells and NK cells and higher proportions of neutrophils (Table 2). To examine the directionality of the association between PTSD symptoms and immune cell type proportions, we leveraged longitudinal samples from three cohorts (MRS, PRISMO, and Army STARRS) that were evaluated before and after military deployment. An increase in PTSD symptoms was associated with a decrease in B cells ($z = -2.67$; $p = 0.008$) over the course of the deployment, but there were no other differences in cell proportions (Table S2).

Next, we examined whether there were cell-type-specific DNA methylation patterns associated with PTSD. The Quantile-Quantile (QQ) plots did not suggest inflation of the test statistics, with lambdas ranging from 0.82 to 1.22 (Fig. S1). Because of the PTSD-associated differences in cell composition (Table 2), our primary hypotheses were that we would detect PTSD-associated DNAm differences in B cells (Table S3), NK cells (Table S4), and neutrophils (Table S5). However, we also performed exploratory analyses of monocytes (Table S6), CD4 + T cells (Table S7), and CD8 + T cells (Table S8). After controlling for multiple testing, 96 CpGs associated with PTSD in a specific immune cell type (Fig. 1): 88 in B cells, five in NK cells, one in CD4 + T cells, and two in CD8 + T cells. No PTSD-associated CpGs were identified in monocytes or neutrophils, and none of the CpGs associated with PTSD in any cell type were identified in prior *meta*-analyses of DNAm in PTSD (Katrinli et al., 2022a; Katrinli et al., 2024; Smith et al., 2020; Snijders et al., 2019; Uddin et al., 2018). Evaluation of the 96 PTSD-associated CpGs (Table S9) and the top 500 CpG sites in each cell type (Tables S10-S15) did not reveal enrichment of any gene ontologies after controlling for multiple comparisons.

Table 2
Differences in estimated cell proportions by PTSD status.

Cell Type	Cases	Controls	Std Beta	t-stat	p-value
B cells	0.05 (0.03)	0.06 (0.03)	−0.061	−3.43	6.1e-4
CD4 + T cells	0.16 (0.05)	0.17 (0.06)	−0.031	−1.74	0.081
CD8 + T cells	0.10 (0.05)	0.10 (0.05)	−0.006	−0.35	0.73
Monocytes	0.08 (0.02)	0.08 (0.03)	0.009	0.53	0.60
NK cells	0.04 (0.02)	0.05 (0.02)	−0.125	−7.00	3.1e-12
Neutrophils	0.56 (0.10)	0.54 (0.11)	0.062	3.45	5.6e-4

Of the 88 CpGs that were associated with PTSD in B cells, 95 % exhibited lower methylation in those with PTSD. For example, methylation of CpGs in *NR3C1* (cg12466613), *RORA* (cg18730873), and *C3* (cg09880791) were all lower in the B cells of participants with PTSD relative to controls ($3.8e\text{-}8 < p < 1.1e\text{-}8$). Of the 71 PTSD-associated CpGs from B cells annotated to a gene, 16 (23 %) exhibited gene-based associations with PTSD in a recent GWAS *meta*-analysis (Nievergelt et al., 2024), a rate that is higher than one would expect by chance ($p < 0.0001$).

3.0.3. Associations of PTSD and cell-type-specific DNAm with C-reactive protein (CRP)

PTSD has been linked to inflammation (Friend et al., 2022), and C-reactive protein (CRP) is a reliable and clinically-utilized indicator of inflammation that can modulate the function of distinct immune cells (Volanakis, 2001), including B cells that were most strongly implicated in our analyses above (Volanakis, 2001; Whisler et al., 1983). We thus next examined CRP levels in a subset of 1077 participants (52.8 % current PTSD) from three cohorts that had measured CRP (GTP, MRS, and NCPTSD/TRACTS). A bivariate analysis that compared CRP levels in PTSD cases and controls neared significance ($z = 1.95$; $p = 0.052$), but a multivariable analysis that controlled for age, sex, and smoking did not support an association between CRP and PTSD ($z = 1.30$; $p = 0.20$). We next tested for association between CRP and cell proportions in these cohorts. Higher CRP levels associated with higher proportions of neutrophils ($z = 4.54$; $p = 5.6e\text{-}6$) and lower proportions of B cells ($z = -2.10$; $p = 0.036$), NK cells ($z = -4.14$; $p = 3.5e\text{-}5$), and CD8 + T cells ($z = -4.47$; $p = 7.9e\text{-}6$).

To understand the role of inflammation in relation to PTSD-associated CpGs, we compared the effect sizes of 1625 CRP-associated CpGs identified in a recent *meta*-analysis of CRP (Wielscher et al., 2022) to the effect sizes of PTSD-associated CpGs from the most recent PGC PTSD Epigenetics Workgroup *meta*-analysis (Katrinli et al., 2024) and observed a strong correlation in effect sizes ($r = 0.72$; $p < 2.2e\text{-}16$; Fig. 2). Interestingly, 699 (43 %) of the CRP-associated CpGs nominally associated with PTSD, which is significantly higher than one would expect by chance ($p < 0.0001$).

4. Conclusions

In the current study, we conducted the largest examination of immune cell composition in relation to PTSD. We found that those with PTSD had higher proportions of estimated neutrophils when compared to trauma-exposed controls. Neutrophils are the most common type of immune cell in peripheral blood. As a key driver of the innate immune response, neutrophils play an important role in responding to and helping to resolve acute inflammation. However, in cases of chronic inflammation, which is reported to occur in PTSD (Friend et al., 2022; Katrinli et al., 2022b), neutrophils further propagate inflammation by releasing immune mediators and by activating other immune cells (Herrero-Cervera et al., 2022). An expansion of neutrophil numbers relative to lymphocytes (neutrophil–lymphocyte ratio, NLR) has been observed in many acute and chronic pathologic conditions, including psychotic disorders and among those reporting childhood trauma and

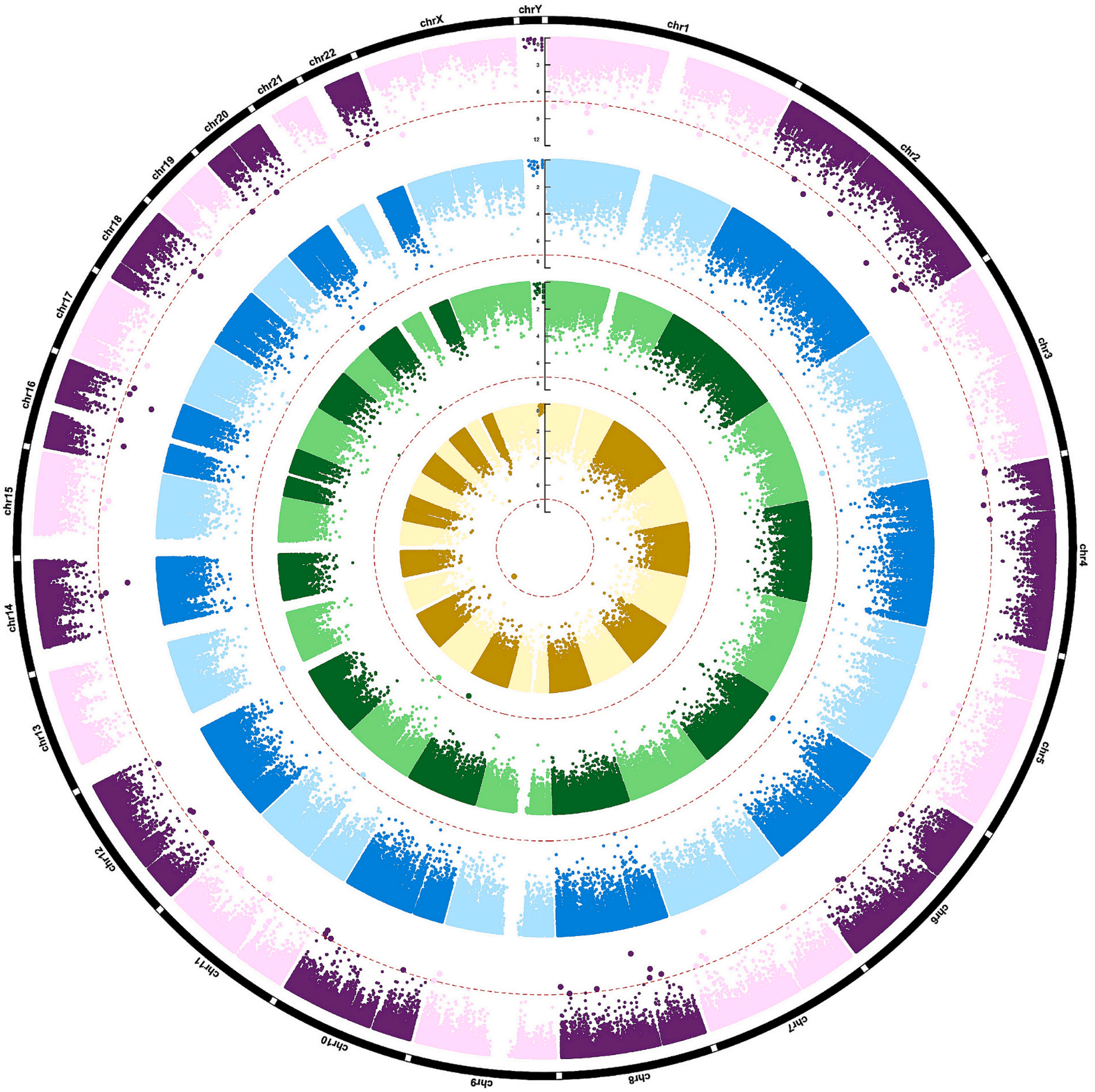

Fig. 1. Overview of the epigenome-wide associations with PTSD in immune cell types. Circular Manhattan plot indicating chromosomes on the outer track followed by the cell-type-specific associations, depicted as − log 10 (p-values), for B-cells (purple track), NK cells (blue track), CD8 + T cells (green track), and CD4 + T cells (yellow track). For each track, the red dashed line indicates the epigenome-wide significance threshold of $p < 9.0\text{e-}8$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

indicate an elevated inflammatory state (Bioque et al., 2022; Cunat et al., 2024). Indeed, multiple prior studies have supported the role of inflammation in PTSD by examining CRP, a molecular indicator of inflammation synthesized in the liver and adipose tissue in response to elevated interleukin 6 (IL-6) levels (Volanakis, 2001).

In the current study, we did not identify an association between PTSD and CRP, though a recent *meta*-analysis of 15 independent studies representing > 4600 participants reported that PTSD cases have higher levels of CRP when compared to controls (Yang and Jiang, 2020). A longitudinal study suggests that higher serum CRP levels prior to deployment predicted post-deployment PTSD symptoms in male veterans (Eraly et al., 2014). However, it has not been clear whether inflammation was a risk factor for the development of PTSD or a consequence of having PTSD. A study by Carvalho and colleagues reports a positive genetic correlation between PTSD and CRP, with further modeling suggesting a causal bidirectional association between the two (Muniz Carvalho et al., 2021). However, Maihofer and colleagues subsequently suggested that the associations between PTSD and CRP are likely due to shared pleiotropy (Maihofer et al., 2024). In the current study, we noted that higher CRP levels are associated with higher proportions of neutrophils and lower proportions of B cells, NK cells, and CD8 + T cells. A recent study identified a group of CpG sites associated with CRP in whole blood and then used Mendelian Randomization to show that alterations in DNAm are likely a consequence of increased CRP levels and not part of the pathway driving inflammation (Wielscher et al., 2022). In our study, which compared the effect sizes of CRP-associated CpGs (Wielscher et al., 2022) to PTSD-associated CpGs from a *meta*-analysis that controlled for differences in cell composition (Katrinli et al., 2024), we noted a strong correlation in effect sizes, supporting that inflammation is chronic in those with PTSD associated with robust DNAm differences. Longitudinal or *in vitro* studies will be required to distinguish whether PTSD drives inflammation that results in

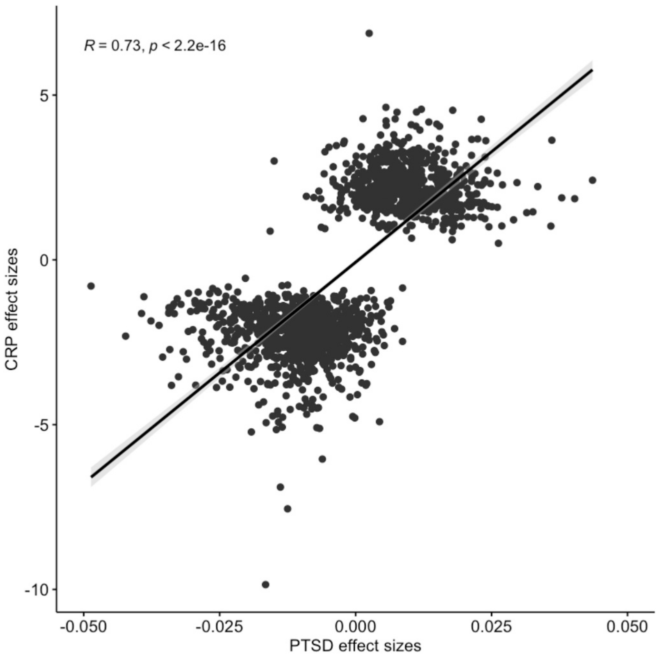

Fig. 2. Correlation of effect sizes between CRP and PTSD in whole blood. CRP was examined as a continuous trait, as described in (Wielscher et al., 2022), while PTSD was examined as a categorial variable, as described in (Katrinli et al., 2024).

DNAm changes or if PTSD drives DNAm changes that promote inflammation.

We found that those with PTSD had lower proportions of estimated NK cells when compared to trauma-exposed controls. Natural killer (NK) are cytotoxic lymphocytes that function at the interface of the innate and adaptive immune responses (Vivier et al., 2011). Multiple studies have proposed that NK cells contribute to PTSD-associated immune impairments (Gotovac et al., 2010; Kawamura et al., 2001; Laudenslager et al., 1998; Mosnaim et al., 1993) including one that identified a subset of dysfunctional NK cells that were more likely to occur in combat-exposed veterans with PTSD than in combat-exposed veterans without PTSD (Bersani et al., 2016). This study also suggested that the frequency of dysfunctional NK cells among those with PTSD was consistent with premature biological senescence or accelerated biological aging, which has subsequently been widely reported in those with PTSD (Aiello et al., 2016; Katrinli et al., 2023; Katrinli et al., 2020; Wolf et al., 2016; Wolf et al., 2018).

The current study also found that those with PTSD had a lower proportion of B cells when compared to trauma-exposed controls. B cells are a primary driver of adaptive immunity, playing a role in regulating the immune response (Klinker and Lundy, 2012). B cells produce antibodies, and, when dysregulated, contribute to autoimmune disorders by producing autoantibodies (Klinker and Lundy, 2012; Yanaba et al., 2008). Interestingly, epidemiological studies suggest that those with PTSD are at higher risk of developing autoimmune disorders including multiple sclerosis and rheumatoid arthritis (Boscarino et al., 2010; O'Donovan et al., 2015; Song et al., 2018). We noted that the proportion of B-cells decreased in those with higher PTSD symptoms over a military deployment. Understanding the immune system response following traumatic stress and in those with PTSD is integral to our understanding of the disease process and its many comorbidities. As aforementioned, heightened inflammatory conditions are indicated by a shift in cellular compositions of greater neutrophil numbers accompanied by lower lymphocyte numbers, which was observed in our investigation in association with PTSD as well as CRP levels. Our results further indicate that NK and B cells, two lymphocyte subpopulations, may be particularly impacted. It is beyond the scope of our investigation, however, to seek functional implications of this phenomenon in PTSD, which warrants a future investigation.

To understand how gene regulation of these different cell types associates with PTSD, we examined cell-type-specific DNAm patterns. PTSD-associated CpGs were identified in B-cells and NK cells, which support that the differences in cell composition associated with PTSD are consistent with epigenetic regulation in those cell types. For example, in B-cells, PTSD associated with a CpG site in *RORA*, which encodes a nuclear hormone receptor that helps to protect cells from the effects of injury, stress and disease and that has been previously implicated in PTSD (Logue et al., 2013). Further, the PTSD-associated CpGs identified in B-cells were much more likely to occur in genes identified in a PGC GWAS for PTSD than would be expected by chance, supporting a link between these changes in peripheral immune cells and genes that contribute to PTSD. These results are consistent with a cell-type-specific study of DNAm conducted in anxiety disorders (i.e. panic disorder, social phobia, agoraphobia, or generalized anxiety disorder) that identified DNAm differences in monocytes and granulocytes, supporting the role of immune dysregulation in psychiatric disorders (Hettema et al., 2023). While these are not the first studies to support immune dysregulation in psychiatric disorders, they are among the first to document the immune cell-type-specific changes in DNAm, suggesting a mechanism through which those with psychiatric disorders could be at increased risk of immune-related health problems.

The study does have some limitations. First, immune cell composition was imputed rather than measured directly. Though the imputation is a highly reliable method that enables use of a large sample size (Teschendorff et al., 2017), physical sorting would likely provide greater resolution. Physical sorting would also enable us to examine absolute cell abundance and not just cellular proportions. Also, CRP levels were only available in a subset of cohorts, so this analysis was not as well powered as the cell type comparison. We did not control for body mass index in our analyses of CRP, as both immune cells and adipocytes produce cytokines that can stimulate CRP release. This study was not able to account for medical comorbidities and their treatment, some of which may have an inflammatory or immune component, because comorbidities were not captured uniformly in most of the individual cohorts. Finally, the cell type specific association results in NK cells exhibited some inflation in the QQ plots, suggesting that those results may include false positives and should be interpreted with caution. Despite these limitations, the current study suggests that those with PTSD experience immune dysregulation and excessive inflammation that not only results in lower proportions of adaptive immune cells, such as B-cells, but also different epigenetic regulation in those cells.

Author contributions

Writing group: AEA, SH, SK, MWL, AXM, CMN, AKS, MU, EJW, and AZ.

Study PI or co-PI: AEA, DGB, CF, EG, RCK, KCK, MWL, SAM, WPM, MWM, CMN, NRN, HKO, SAMR, KJR, VR, AKS, DJS, MBS, MU, RJU, EV, and DEW.

Obtained funding for studies: MPB, CF, EG, RCK, KCK, MWL, SAM, CMN, NRN, HKO, SAMR, KJR, BPFR, AKS, MU, RJU, EV, and AZ.

Clinical: CF, JG, EG, CG, NK, MWL, AP, SAMR, KJR, JWS, EV, and EJW.

Contributed data: CF, NF, CG, JPH, SK, APK, IL, MWL, VM, WPM, MWM, CMN, NRN, AP, SAMR, AKS, MBS, MHV, and EJW.

Statistical analysis: MPB, LB, C-YC, SD, SK, APK, IL, MWL, AXM, MSM, CMN, BPFR, AKS, CHV, AHW, EBW, EJW, and YZ.

Bioinformatics: MPB, LB, C-YC, SDL, MWL, AXM, BPFR, EJW, and YZ.

Genomics: MPB, SDL, BPFR, CHV, and AZPIs of the EWAS group: MWL, CMN, AKS, and MU.

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Funding

This work was supported by the National Institute of Mental Health (NIMH; R01MH108826 and R01MH106595). The cohorts were also supported by the following grants from NIH, the Department of Veterans Affairs, the Department of Defense, the Netherlands Scientific Organization, Dutch Research Council (NWO): I01BX003477 (MWL), 1I01CX001276 (EJW), R01MD011728 (MU), R01MH105379 (NRN), R15MH099521, 5R21MH085436, R15HD049907 (HKO), W81XWH-11-1-0073 (SAMR), BX005872 and CX002343 (VBR), 91718336 (BPFR), 09150171910042 (CHV), R01MH111671 (NF), R01AG058822 (JPH), K12HD085850 (SK). Additional support was provided by the South African Medical Research Council and the Bill and Melinda Gates Foundation (OPP 1017641; DJS and NK); the US Army MRMC, One Mind, and the Mayday Fund (SAM), and a Foundation of Hope Advanced Seed Grant (ASZ).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Chia-Yen Chen is an employee of Biogen. Dr. Koenen has done paid consulting for the US Department of Justice and Covington and Burling, LLP. She receives royalties from Oxford University Press and Guilford Press. Dr. McLean has served as a consultant for Walter Reed Army Institute for Research, Arbor Medical Innovations, and BioXcel Therapeutics, Inc. Dr. Nugent is an unpaid member of the scientific advisory board for Ilimivu. Dr. Rauch receives royalties from Oxford University Press and American Psychological Association Press and serves on the Advisory Panel for Otsuka Pharmaceuticals. Dr. Ressler has performed scientific consultation for Bioxcel, Bionomics, Acer, and Jazz Pharma; serves on Scientific Advisory Boards for Sage, Boehringer Ingelheim, Senseye, and the Brain Research Foundation, and he has received sponsored research support from Alto Neuroscience. DJS has received consultancy honoraria from Discovery Vitality, Johnson & Johnson, Kanna, L'Oreal, Lundbeck, Orion, Sanofi, Servier, Takeda and Vistagen. All other authors declare no interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2025.04.031.

Data availability

Data will be made available on request.

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