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Post-traumatic stress disorder and potential biomarkers: a critical review

Abstract

Posttraumatic Stress Disorder (PTSD) is introduced by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5 TR) (2022) as a mental health condition that impacts approximately 6.8% of U.S. adults. Despite the abundant literature on the psychological underpinnings of PTSD, biological mechanisms are not well understood. Additionally, critical reviews are far and few between with regard to physiological research on PTSD. As such, it is crucial to explore the underlying biological mechanisms in addition to the psychological elements of PTSD etiology. Biomarkers are introduced as a potential indicator for exploring physiological and psychological symptoms, distinguishing diagnosis, and predicting symptom severity, intensity, and duration. While research supports biomarkers as an accurate indicator for understanding PTSD pathology, a clinically validated biomarker test has yet to be developed. This critical review evaluates the relevant literature related to biological markers and PTSD to identify strengths, limitations, and future directions in biomarker research as it relates to PTSD etiology. This critical review reveals that despite the robust internal and validity methods in biomarker PTSD research, the methodologies are limited in the scope of generalizability, inclusion of diversity and intersectionality interactions, and flexibility for complex presentations. Much of the literature also fails to incorporate treatment directions or clinical application suggestions, as much of the biomarker findings are too vague or complex for accessible implementation. Despite the limitations in methodology, this critical review concludes that biomarkers are the first step in facilitating an integrative and holistic approach to our understanding of PTSD pathology. Future directions include the application of biomarker research on PTSD treatment, progression of symptomology, prevention, and protective factors, and the development of a universal biomarker test for PTSD that is generalizable.

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Introduction

Posttraumatic stress disorder and prevalence

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5 TR) (2022) describes Posttraumatic Stress Disorder (PTSD) as a trauma-related disorder that impacts around 6.8% of U.S.[1] adults. PTSD is characterized by:

A. traumatic stimuli that are directly experienced, witnessed, or learned;

B. intrusive symptoms (e.g., involuntary recurring memories, flashbacks, nightmares);

C. avoidance symptoms (e.g., avoidance of trauma stimuli including locations, specific individuals, or other activities);

D. arousal symptoms (e.g., hypervigilance, heightened startle response, irritability);

E. symptom duration of at least one month;

F. significant dysfunction/impairment socially or professionally; and

G. the disturbances are not attributable to another condition.

The prevalence of PTSD is relatively increased among veterans and survivors of military combat/captivity. Other findings suggest that the prevalence of PTSD may range between 10 to 25% in military populations depending on the study, gender, and deployment experience.[2–4] In a more recent umbrella review, Schincariol et al.[5] suggest there is an overall prevalence rate of PTSD of 23.95 percent (with a 95% confidence interval between 20.74 and 27.15). Schincariol and colleagues[5] state that true prevalence rates range from as low as 2.5 percent to as high as 74 percent depending on the nature of the traumatic event, assessment methods in research, demographic, cultural, or other identity variables, and severity of exposure. Despite the comprehensive literature on the prevalence and psychological outcomes of PTSD, the physiological underpinnings of PTSD are not well understood.[6,7]

Background on biological factors of PTSD

One such article by Bulut and colleagues[6] conducted a systemic review on the biological bases of PTSD and physiological outcomes. The authors cite cardiovascular problems (e.g., hypertension, heart disease, tachycardia), metabolic and immune system dysregulation (e.g., increased risk of diabetes, chronic fatigue, autoimmune disease), neurological and endocrine changes (e.g., altered cortisol levels, dysregulation in norepinephrine and epinephrine secretion), Musculoskeletal issues (e.g., arthritis, skeletal fractures), gastrointestinal disorders (e.g., chronic pain, gastritis), respiratory issues (e.g., respiratory distress, difficulty breathing), brain changes (e.g., potential hippocampal atrophy, decreased memory and task-switching functioning due to structural and functional brain changes), and other health risks (e.g., obesity, increased risk of cancer, liver disease, and stroke). While this list is not conclusive, this research demonstrates the significant negative impacts on overall health. **Biomarkers** are introduced as a potential indicator for assessing and understanding the physiological and pathological factors related to PTSD pathology. Biomarkers are analyzed from biological samples (e.g., saliva, blood, cerebrospinal fluid (CSF), urine, and tissues) and can identify hormones, neurotransmitters, and genetic factors that help understand the severity, intensity, and duration of PTSD pathology.

Despite the recent influx of biomarker research on PTSD, the authors concluded that, to date, no one has developed a clinically validated biological marker test for PTSD. Additionally, there are limited published critical review papers on the biological systems linked to PTSD etiology.[7] This critical review aims to evaluate some of the recent literature on biomarkers to identify strengths, limitations, and future directions in biomarker research pertaining to PTSD pathology.

Critical review

Biological correlates predictive of PTSD severity and symptomology

Siegel and colleagues[8] attempted to use machine learning in a cross-sectional study to review biological markers associated with two different severity types of PTSD: subtype 1 (S1) with a mean Clinician-Administered PTSD Scale (CAPS) score of 54.3 and subtype 2 (S2) higher severity PTSD group with a mean CAPS score of 75.6. The two severity types were created via the Partitioning Around Medoids (PAM) clustering method used in the machine learning proximity matrix.

Siegel et al.[8] hypothesized that machine learning would accurately identify symptom severity in military-related PTSD subtypes and biological correlations. The participants in the study (male Iraq and Afghanistan veterans) were gathered from the PTSD Systems Biology Consortium. They included a discovery sample of 74 individuals with PTSD and 71 healthy controls (HC), as well as a validation sample of 26 individuals with PTSD and 36 HC. PTSD diagnosis was based on the DSM-IV criteria with CAPS scores equal to or greater than 40. Symptom severity was assessed using 16 distinct validated clinical scales, including the CAPS and other self-report assessments. Exclusion criteria include anyone who had psychological comorbidities or prominent suicidality. Biological, clinical, and neurocognitive data on this population were evaluated 6-10 years post-deployment.

According to Siegel et al.,[8] blood was drawn to collect one million+ biomarkers, including GWAS, DNA methylation, miRNAs, metabolomics, proteomics, small molecules, endocrine markers, routine clinical lab panels, and biometric/physiological markers. A mixed-methods design labeled "wisdom of crowds" was used to reduce features into 343 unique candidates, then further reduced to 28 fundamental biomarkers. Random Forests (RF) machine learning was used to quantify similar clinical constructs of participants and separate them into two subtypes (S1 and S2). The validation process included performing bootstrap sampling within the RF model as well as scoring the RF model with an independent validation sample. Differences between subtypes were analyzed via ANOVA and Wilcoxon rank-sum tests for clinical and biomarker variables. A canonical correlation was used to evaluate patterns between identified biomarkers and PTSD features.

Siegel et al.[8] stated that five core biomarkers were found to be significantly correlated with PTSD, including Lactate, GORASP2, BRSK2, miR-106b, and miR-93. Biomarkers were also effective in differentiating the less severe subtype (S1), more severe PTSD subtype (S2), and HC. More specifically, lactate was significantly elevated in the S2 group, demonstrating a link between metabolic stress and high physiological arousal and cellular stress responses. DNA Methylation Markers such as GORASP2 and BRSK2 (i.e., genes linked to cellular stress mechanisms such as apoptosis and neurological functioning) were downregulated in S2. MicroRNAs such as miR-106b and miR-93 (gene expressions linked to stress response and cellular functioning) were downregulated in S2 compared to S1 and HC. Overall, biomarkers were able to develop individualized profiles for S1 and S2, where S2 indicated significantly more severe biomarker dysregulation linked to stress response, neurobiological health, and systemic inflammation relative to S1 or HC. In contrast, S1 indicated a moderate biomarker dysregulation profile. Machine learning was effective in predicting the biological underpinnings of PTSD symptom severity and physiological outcomes.

Methodological strengths and limitations

The Siegel et al.[8] study holds strengths in that it provides evidence that PTSD pathology may be a multi-systemic disorder with stress responses that can be observed from a cellular level. The authors used a robust advanced machine learning approach (RF and PAM) for subtyping PTSD outcomes based on clinical and biomarker data, which limited human error and enhanced the accuracy of the analysis. The authors also chose to use 16 validated clinical scales integrated with biological data to provide a holistic analysis of PTSD that many studies fail to accomplish. Validation efforts were evident with the bootstrap resampling method to ensure an accurate estimation of classification errors and accuracy. It is also worth noting that the authors selected a high-risk group for PTSD, which promotes insight and exploration into the PTSD etiology of an underserved population.

Despite targeting an underserved population, the small sample size in the Siegel et al.[8] article limits the generalizability of the results. Excluding female and non-binary participants may also restrict the applicability of the findings. Critics may argue that limiting the sample to military veterans only provides a narrow scope of the findings to a very niche group that may not be replicated with civilians or other populations with PTSD. The findings in the study did not link any conclusions to treatment directions, which may limit the exploration of future directions with the data.

There are several other methodological limitations outside the participant criteria. Siegal et al.[8] did not include other previously researched markers, such as neuroimaging or EEG markers, limiting the scope of the neurological conclusions of the neurological underpinnings of PTSD. Furthermore, the clustering method used in the study was limited to only two subtypes and a control group based on the sample size constraints, which may create an issue with heterogeneity. The authors also selected participants who experienced their traumatic event 6-10 years prior, limiting potential findings of early subtyping closer to the time of exposure. Finally, the authors utilized a cross-sectional approach, which limits any conclusive evidence about causal relationships between the severity of PTSD and reported biomarkers.

Biological markers for validating warzone-related PTSD diagnosis

Dean et al.[9] conducted another cross-sectional study with longitudinal components in which researchers attempted to review the biological markers that are associated with diagnosing and validating warzone-related PTSD diagnoses. The authors theorized that utilizing biological markers would provide success in diagnosing and validating warzone-related PTSD in U.S. Military veterans. The researchers focused their recruitment efforts on male veterans between the ages of 20 and 60 who served in combat during Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). The 165 participants were split into either a PTSD-positive group (n = 83) (individuals with warzone-related PTSD) or a PTSD-negative group (n = 82) (trauma-exposed controls with no PTSD diagnosis). All participants were screened for PTSD via the Structured Clinical Interview for DSM (SCID) and CAPS. PTSD-positive veterans had

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PTSD for at least three months with a minimum CAPS score of 40. In contrast, PTSD-negative veterans had no lifetime history of PTSD and a CAPS score of less than 20. The exclusion criteria for the study included any severe medical conditions, neurological disorders, or significant substance use disorders. Recruited participants also completed assessments related to mood, anxiety, and substance use disorders.

According to Dean et al.,[9] over one million blood samples were collected from participants to evaluate genetics, methylomics, proteomics, metabolomics, immune cell counts, cell aging, endocrine markers, microRNAs, cytokines, and more. DNA methylation was quantified using a genome-wide unbiased approach as well as a targeting sequencing-based approach. 343 biomarkers were identified using a "wisdom of crowds," similar to the Siegel et al.[8] study. 55 participants were re-evaluated around three years (3.3 +/- 0.9 years) post-baseline assessment to evaluate symptom changes over time (15 PTSD-positive individuals, 11 subthreshold PTSD individuals, and 29 controls). A validation cohort of a new set of participants was used to validate the identified biomarkers (26 PTSD-positive individuals and 26 controls). The researchers conducted a two-stage down-selection process based on the area under the curve (AUC) and the variable importance of reducing the panel to 28 biomarkers. Biomarkers were extracted and tested from the validation cohort using RF.

The data in the Dean et al.[9] study were analyzed via AUC to assess the predictive performance of the biomarkers and whether they could distinguish the two groups (PTSD-positive versus PTSD-negative). Similar to the Siegel et al.[8] study, a bootstrap method was used to validate the sensitivity, specificity, and accuracy of the findings. A Pearson's correlation coefficient demonstrated moderately significant effects between predicted PTSD and total CAPS scores as well as PTSD scores and PTSD symptom clusters (e.g., re-experiencing, avoidance, and hyperarousal). The AUC result (0.80) demonstrated that the 28 biomarker panel had a strong diagnostic performance.

Dean et al.[9] concluded that 28 biomarkers derived from multi-omic data (e.g., DNA methylation, proteins, microRNAs, and metabolites) could be utilized to diagnose combat-related PTSD with significant accuracy in male veterans. The authors highlight strength of biomarker paneling, which may reduce bias in the diagnosing process that is often a limitation of other diagnostic methods (e.g., self-report measures, clinical observation). In addition to distinguishing PTSD cases from the control group, the moderately positive correlation ($r = 0.59$) showcases that the 28 biomarkers can also help with distinguishing the severity of symptoms. The researchers stated that in their longitudinal results, there was an emergence of a subthreshold PTSD group in which some participants who were initially in the PTSD-negative group developed subthreshold PTSD symptoms during the 3 year follow-up period, suggesting that PTSD can either have delayed onset or can evolve over time. In contrast, some individuals in the recall cohort demonstrated reduced symptoms of PTSD. An evaluation of the performance of biomarkers in predicting changes suggested that such changes in PTSD presentation could be effectively tracked or predicted via the 28 biomarker panel. Finally, the identified biomarkers were related to neurological, immune, stress, and cardiovascular pathways, supporting the relevant literature on the biological underpinnings associated with PTSD pathology.[6,7,10,11]

Methodological strengths and limitations

The Dean et al.[9] study is similar to the Siegel et al.[8] study, so there is overlap in some of the strengths and similarities in the review of the methodology. For example, both studies implemented a robust machine learning program (RF) to effectively validate the accuracy, sensitivity, and specificity of the results with a smaller margin for human error. The Dean et al.[9] study also integrates both psychological (i.e., via CAPS assessment and other PTSD scales) and biological sources (e.g., genomics, proteomics, metabolomics) to enhance the holistic understanding of PTSD etiology. Additionally, the participants consisted of male military veterans, limiting the scope of generalizability of the study and promoting understanding of a traditionally underserved and high-risk population. This study also implemented a bootstrap methodology for improving internal validity.

One distinction from the Dean et al.[9] study was the implementation of a longitudinal component to explore PTSD development over time, which many studies fail to do. However, all cohorts failed to include any individuals outside of the military or other gender identities. Another limitation for both the Dean et al.[9] and Siegel et al.[8] study is the lack of inclusion of cultural, racial, ethnic, and other identity information and how it may impact findings. While the Dean et al.[9] study has a larger ($n = 281$) sample size, it is hard to say whether the developed biomarker panel may be able to successfully predict the same outcomes in individuals with other identities or presentations. Selection bias is another concern, as recruitment may have been too narrowly focused on a specific population who may be more eager to participate. Curiosity is also raised with regard to biomarkers as a whole since biological mechanisms are often complex and multi-faceted.[6] In other words, one biomarker may indicate multiple factors both within and outside the PTSD spectrum, creating a convoluted profile of an individual who may be experiencing comorbidities. The study excluded individuals who may be experiencing other mental or physical complications, so it is difficult to say how biomarkers may interact with a more complex case study, especially considering humans are complex individuals and many PTSD presentations are often comorbid with other presenting challenges.[1] Lastly, it is worth noting that both Dean et al.[9] and Siegel et al.[8] relied on DSM-IV criteria, which have since been updated to the DSM-5-TR, limiting the applicability of results under the updated standard manual for diagnoses.

Diagnostic biomarkers and targeted drugs for stress disorders

Le-Niculescu et al.[12] offer a refreshing approach to diagnostic biomarker research for stress-related disorders in that they offer some insight into the treatment potential associated with biomarker technology. The authors attempted to identify blood gene expression biomarkers for psychological stress as well as identify the potential for targeted PTSD drug-based treatment. The researchers hypothesized that biomarkers would be a valid and accurate method for determining the diagnosis of stress-related disorders.

Similar to the prior studies, Le-Niculescu et al.[12] developed three cohorts: (1) a discovery cohort consisting of 36 participants (28 male and eight female psychiatric participants with at least one switch between low stress and elevated stress state measured via the Visual Analogue Scale (VAS)), (2) a validation cohort (35 male and 27 female psychiatric participants), and (3) an independent testing cohort broken into three sub-cohorts: 95 males and 27 females evaluated for predicting stress states; 144 males and 18 females for predicting future stress-related hospitalizations in the first year following assessment; 166 males and 20 females for predicting future stress-related hospitalizations in all years following initial assessment. All participants were recruited from the patient population at the Indianapolis Veterans Affairs (VA) Medical Center. Participants completed diagnostic interviews for genetic studies for up to six testing visits around three to six months apart or whenever a psychiatric

hospitalization occurred. Each testing visit included a series of scales, including a self-report visual analog scale for stress, PTSD checklist (PCL-Civilian), and blood sampling conducted to evaluate relevant biomarkers. A validation cohort was created to validate biomarker findings. The testing cohort was used to predict future stress-related hospitalization visits.

According to Le-Niculescu et al.,[12] changes in low and high-stress states were evaluated via longitudinal within-subjects design. Biomarkers were filtered with a Convergent Functional Genomics (CFG) approach, which attempted to integrate previously published human and animal model evidence in the field and directly cite the data. The top biomarkers that were identified from the discovery cohort were then validated in a new independent cohort of psychiatric participants with high scores on the VAS clinical stress rating scale. The researchers tested whether the candidate biomarkers from other cohorts were able to predict high-stress states and future psychiatric hospitalizations in a third independent cohort of psychiatric participants. Data was analyzed based on gender and psychiatric diagnosis, resulting in increased accuracy with a personalized approach. The researchers analyzed the biological pathways and relevant networks to identify whether there was a link between biomarkers and other psychiatric and related disorders. The final step involved evaluating the biomarkers as targets for existing drugs that can be used as personalized treatment and treatment response.

The study by Le-Niculescu et al.[12] was statistically analyzed in several unique ways. Gene expression data was assessed using a robust multi-array analysis (RMA) by gender and diagnosis. An ANOVA was conducted to evaluate whether the expression changes were significant across the different groups (e.g., low stress, high stress, clinically severe stress). The receiver operating characteristic (ROC) curve and AUC scores determined the biomarker's performance. Pearson's correlation and t-tests evaluated links between biomarker levels and stress measures. For the longitudinal analysis, a Cox regression evaluated the timing related to hospitalizations.

The major findings of the Le-Niculescu et al.[12] study supported the previous literature in that multiple gene expression biomarkers can accurately and effectively predict high-stress states as well as future psychiatric stress-related hospitalizations. The biomarkers identified also support previous literature in that the majority of the biomarkers were linked to pathways and systems involving human stress response, immune function, inflammation activation, and stress-related cellular processes. Some of the identified markers include FKBP5 (regulates glucocorticoid receptor activity), DDX6 (modulator for stress regulation and composition), B2M (associated with cell regulation and kidney function), LAIR1 (linked to inflammatory process), RTN4 (linked to injury recovery of the central nervous system), and NUB1 (mitigates degradation of proteins) which are strongly associated with stress function. Over 50 percent of the observed biomarkers were linked to other literature involving suicide and other psychiatric disorders. In terms of treatment, several existing drugs and natural remedies (e.g., botulin and calcium folinate) were identified as treatment candidates for the identified biomarker profiles, suggesting potential in the sector of developing targeted treatment programs for stress-related disorders.

Methodological strengths and limitations

Le-Niculescu et al.[12] attempt to fill some of the gaps that have been identified in the previous studies by Dean et al.[9] and Siegel et al.[8] For instance, Le-Niculescu et al.[12] include female participants in their study. Additionally, the authors do not exclude comorbidities or limit their presentation to individuals with a PTSD diagnosis. This study, in particular, uses stress-related pathology as its' inclusion criteria, allowing for more generalizable presentations that may be more accurate depictions of what someone may present with. Another strength related to methodology is that the researchers use a within-subjects design, which limits inter-individual variability by comparing different stress state data with the same participants. This method reduces potential confounds such as genetic background, lifestyle, or medication differences. The validation process was also strength of this study. The authors incorporated a discovery, prioritization, validation, and testing phase across distinct groups of participants, increasing the reliability and overall generalizability of the results. This process also provided increased opportunity for diversity amongst participants, which helped account for variance in the diagnosis presentation. The inclusion of targeting drug mechanics made this study stand out amongst the other articles in this review, as it provides future directions for implementing treatment protocols that may benefit this population and presentation.

The Le-Niculescu et al.,[12] study may have incorporated female participants. However, the sample size is still relatively small compared to the males in the study (324 males compared to 68 females amongst all cohorts). Additionally, breaking the sample sizes into relatively small groups (e.g., 36 subjects in the discovery cohort) likely resulted in a smaller statistical power and increased the risk of type I errors. Another methodological limitation was the recruitment strategy. Participants were only recruited from a single medical VA center, limiting the generalizability to non-psychiatric or non-veteran populations. As such, the results of this study may not be reliable in predicting the same outcomes amongst civilian or non-psychiatric individuals. Another shortcoming is that although the authors used a within-subject design, participants were on a variety of psychiatric and non-psychiatric medications, which the authors state may have confounded the gene expression data. It is also worth noting that similar to Dean et al.[9] and Siegel et al.,[8] this study includes the use of self-reported measures, which may be beneficial in terms of practicality and ease of use but are limited in their own right due to increased risk of recall and response biases. Furthermore, these self-report surveys are a snapshot of a client's presentation at a specific time and should not be solely used to inform a formal diagnosis without supplemental data from clinical observation, non-structured interviews, and supervision.

The Le-Niculescu et al.,[12] study may also be limited because the authors compared their predictive biomarker results to benchmark telomere lengths (i.e., the length of DNA sequences at the ends of chromosomes to identify the cell's lifespan) as a reference point in an attempt to assess whether the biomarkers were effective in predicting stress states and symptoms. While previous literature supports benchmark telomere lengths as predictive of stress, there is also significant biological variability in which telomere length can be impacted by several elements beyond stress (e.g., age, genetics, lifestyle, illness). This supports the idea that although biomarkers may provide some insight and utility, there is still a significant amount of complexity that may not be completely understood. Researchers may also argue that focusing on a binary construct of high-stress versus low-stress states may limit the study's variability and importance of moderate stress variations. Despite these limitations, this review acknowledges the study's attempt at personalization in predictive biomarkers and treatment outcomes.

Genetic risk factors related to re-experiencing of trauma

In a 2019 study by Gelernter and colleagues,[13] researchers sought to explore the genetic risk factors relevant to intrusive reexperiencing

of trauma in a sample of genotyping data from approximately 165,000 US Military veterans (146,660 European Americans (EA) and 19,983 African Americans (AA)). The authors hypothesized that genetic risk factors relevant to intrusive reexperiencing of trauma would align with previous literature, including genetic correlations, gene-based correlations, metabolism, and more (e.g., the authors stated that the TCF4 biomarker was previously researched to be associated with PTSD and other psychiatric disorders). All the study participants were previously enrolled in the Million Veteran Program, a mega-biobank, to study genetic influences on health and disease. Enrollment involved providing a blood sample, accessing previous health records, and completing questionnaires (e.g., Posttraumatic Stress Disorder Checklist (PCL).

Gelernter et al.,[13] analyzed the blood samples and conducted a linear regression analysis with variables such as sex, age, and principal components (PCs) to account for differences in individual identities. The authors focused on the reexperiencing symptom cluster of PTSD (e.g., flashbacks, nightmares) as measured by the PCL assessment for phenotyping. The authors used a customized Affymetrix Axiom Biobank array with approximately 723,305 biomarkers for genotyping. Gene-based analysis was conducted via Multi-marker Analysis of GenoMic Annotation (MAGMA). Genotyping and linkage disequilibrium score regression (LDSC) (i.e., a method that attempts to identify heritability and linked genetic patterns from a dataset) were completed to investigate shared molecular mechanisms. MAGMA and LDSC were also used to identify correlations with specific locations of the brain as well as cell types. Gene sets were analyzed to explore biomarker pathways using Ingenuity Pathway Analysis (IPA) and STRING analysis. Finally, the results were validated in a similar fashion as the prior studies by using an independent cohort (i.e., this study validated their results from a United Kingdom Biobank cohort (n = 117,900) using data collected from a PTSD-related question.) The validation supported consistency in genetic risk between cohorts.

According to Gelernter et al.,[13] eight genome-wide biomarkers were identified in the EA cohort as being significantly associated with PTSD: CRHR1 (a gene linked to corticosteroid signaling and stress activation), HSD17B11 (linked to steroid hormone metabolism functioning), TCF4 (Linked to CNS development and schizophrenia pathology), MAD1L1 (previously linked to schizophrenia and personality disorders), KCNIP4 (linked to neuronal excitability, brain signaling, potassium and calcium signaling), CAMKV (linked to intrusive reexperiencing in PTSD, synaptic plasticity and signaling pathways in the brain), LINC01360 (identified as a long intergenic non-coding RNA which is linked to brain function and stress response pathways), and SRPK2 (linked to cell cycle control and apoptosis which may increase neural vulnerability under stress activation). The authors identify a theme in which biomarkers linked to steroid signaling and metabolism may have biological underpinnings linked to the stress-response pathways of PTSD. Five of the eight biomarkers were replicated in the UK Biobank validation cohort, with TCF4 showing the strongest replication. These results also point to significant associations with PTSD and dysregulated biological systems, including the amygdala, hippocampus, hypothalamus, prefrontal cortex, and the striatum. Furthermore, the authors state there were significant gene correlations with other non-PTSD psychiatric traits, including neuroticism, depression, schizophrenia, and insomnia. PTSD biomarkers were also linked to cardiovascular disorders, CNS, and immune function. The authors concluded that their results may promote the future development of targeted treatment protocols based on developed genetic profiles via genetic biomarkers, similar to the study by Le-Niculescu et al.[12]

Methodological strengths and limitations

One of the standout methodological features in the Gelernter et al.[13] study is the large sample size of 165,000. This is strength in terms of statistical power that none of the other studies reviewed came close to having. The majority of the participants (~146,660) were European American, which grants statistical power and increased generalizability for the findings of effectively and accurately detecting genetic biomarkers for this population. Even though there were relatively fewer African Americans (~19,983), this sample size is still relatively large compared to the previously reviewed studies.

In the article by Gelernter et al.,[13] an independent validation cohort (UK Biobank) replicated the results of the study, providing additional support for the accuracy of the identified biomarkers as well as generalizability. Another strength of this study includes the use of several comprehensive analysis protocols, including a single variant analysis (GWAS), gene-based association testing (MAGMA), tissue and cell-type analysis, and biomarker network analysis (IPA and STRING). The researchers were also diligent in observing genetic correlations and biological pathways to identify how physiological systems such as steroid signaling, CNS development, and immune system functioning are directly linked to PTSD pathophysiology. Such results support prior research on biological systems related to PTSD.[6,10]

The authors of the Gelernter et al.[13] study also chose to use the PCL for self-reported re-experiencing symptoms. This serves as strength because it is a validated measure and kept the methodology relatively simplistic for capturing the reexperiencing symptom cluster of PTSD. The downfall of this method is that it may not encapsulate the entire picture or complexity of a PTSD presentation. As stated previously, the self-report method may also lead to measurement errors and reporting bias, discrediting the reliability of the established phenotype in the study.

Going back to the topic of the participants in the Gelernter et al. article,[13] despite having a large sample size, the ethnic representation was disclosed as a binary construct between European Americans and African Americans. No additional ethnic, racial, cultural, sexual, or gender identities were explored or disclosed in the study, limiting our understanding of the relationship between the identified biomarkers and identity expression. This serves as a potential opportunity for future research. Another limitation with regard to the PCL assessment measure is that, unlike the other studies in this review, the authors only used a single question from a single self-report assessment, creating a questionable understanding of self-reported reexperiencing symptoms and an oversimplified phenotype measurement. The other reviewed articles also include some components related to trauma severity, whereas Gelernter et al.[13] do not. This study also does not include a longitudinal component that may be a critical factor related to the onset, progression, and prognosis of PTSD symptoms. Some may argue that because this study is limited in terms of incorporating environmental trauma-related factors (i.e., symptoms severity, duration, frequency), the findings may be limited in scope for furthering our understanding of PTSD risk and gene-environment interactions.

Gelernter et al.[13] also focused their study on common variants (e.g., SNPs) (i.e., minor allele frequency was less than 0.01), which serves as another methodological limitation that may lead to rare genetic variants being unaccounted for. The authors cite another methodological challenge with regard to the relatively smaller sample size and genetic diversity in the African American cohort. This disparity created a challenge in identifying significant biomarker and trans-ancestry associations. This serves as an ongoing issue with a

body of research that is typically Eurocentric to begin with, so it is worth noting the effort to include minority populations in this study regardless of the limitations.

In the Gelernter et al. study,[13] it is worth noting that the reliance on pre-existing databases and models may be limited in capturing the full scope of PTSD-specific biology. The authors relied on IPA, STRING, and MAGMA, which aggregate pre-existing information pertaining to genes, proteins, and bio-pathways. Such information is often obtained through research related to other diseases or biological mechanisms. Because PTSD is understood as a complex disorder, the databases may not include information that is PTSD bio-specific, leading to gaps in the interpretation methodology. As such, authors can only generalize their biomarker pathway findings while being limited in pinpointed biomarker mechanisms unique to PTSD. It may serve the PTSD biomarker research community to begin to develop a dataset of pre-existing biomarker data that are unique to PTSD (e.g., trauma-exposed cohorts or PTSD/stress-specific gene expression biobanks). The results of this study may not be definitive, but they can serve as a blueprint for future research directions on PTSD-specific data.

Conclusion

While biomarkers can be a critical tool for expanding our understanding of PTSD and its psychological and physiological underpinnings, it is an ongoing challenge to develop a universal and comprehensive database that encompasses PTSD uniquely. PTSD has been linked to several physiopathologies, including cardiovascular, metabolic, and immune system dysregulation, musculoskeletal issues, gastrointestinal disorders, brain changes, and more.[6] The studies in this review identify several key biomarkers that link PTSD pathology to biological systems such as the immune system, CNS, hippocampus, prefrontal cortex, and more. In the review, Dean et al.[9] and Siegel et al.[8] were able to identify key biomarkers for diagnosing PTSD and predicting symptom severity. Despite both articles having robust internal validity, generalizability was an issue due to smaller sample sizes, and no inclusion of female participants or non-military related PTSD. The Le-Niculescu et al.[12] study findings offer predictive biomarkers for PTSD diagnosing as well as targeted drug treatment opportunities, which may serve as a unique treatment approach in that each drug protocol is uniquely designed for each individual biomarker profile. Despite the promise, the methodology is limited due to a lack of diversity in its' participant sample (e.g., participants were recruited solely from a VA psychiatric hospital, and the majority of participants were male). The Gelernter et al.[13] study provides a relatively large sample size in their biomarker research and are able to identify PTSD biomarkers that support previous research (e.g., significant associations with PTSD and dysregulated biological systems, including the amygdala, hippocampus, hypothalamus, prefrontal cortex, and the striatum.). The Gelernter et al.[13] study has methodological limitations based on the use of a pre-existing biobank to interpret results and the overrepresentation of European Americans over African American populations in the sample. All of the studies reviewed in this paper are also limited on the basis of utilizing self-report measures for identifying PTSD symptomology, which is subject to measurement errors and bias. The reviewed studies may not provide a comprehensive and definitive list of biomarkers and biomarker utility, but they serve as hypothesis-generators for future direction in the sectors of biomarker treatment research, PTSD biomarker relationships to diverse intersectional identities, and PTSD biomarker research integrated with neuroimaging and other biological evaluation mechanisms.

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