Archival Report

Biological Psychiatry: GOS

Integration of Metabolomic and Brain Imaging Data Highlights Pleiotropy Among Posttraumatic Stress Disorder, Glycoprotein Acetyls, and Pallidum Structure

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ABSTRACT

BACKGROUND: The development of posttraumatic stress disorder (PTSD) is attributable to the interplay between exposure to severe traumatic events, environmental factors, and biological characteristics. Blood and brain imaging markers have been associated with PTSD. However, to our knowledge, no study has systematically investigated the genetic relationship between PTSD, metabolic biomarkers, and brainwide imaging.

METHODS: We integrated genome-wide data informative of PTSD, 233 metabolic biomarkers, and 3935 brain imaging-derived phenotypes (IDPs). Pleiotropy was assessed by applying global and local genetic correlation, colocalization, and genetically inferred causality.

RESULTS: We observed significant genetic overlap between PTSD and glycoprotein acetyls (GlycA) (a stable inflammatory biomarker) in 2 independent cohorts (discovery $r_g = 0.26$, $p = 1.00 \times 10^{-4}$; replication $r_g = 0.23$, $p = 5.99 \times 10^{-19}$). Interestingly, there was no genetic correlation between anxiety and GlycA ($p = .33$). PTSD and GlycA were both genetically correlated with median T2* in the left pallidum (IDP-1444: $r_g = 0.14$, $p = 1.39 \times 10^{-5}$; $r_g = -0.38$, $p = 2.50 \times 10^{-3}$, respectively). Local genetic correlation between PTSD and GlycA was observed in 7 genetic regions ($p < 2.0 \times 10^{-5}$), mapping genes related to immune and stress response, inflammation, and metabolic processes. Furthermore, we identified 1 variant, rs12048743, with evidence of horizontal pleiotropy linking GlycA and IDP-1444 ($z_{IDP\text{-}1444} = 17.14$, $z_{GlycA} = -6.07$, theta $p = 2.06 \times 10^{-8}$). Regional colocalization was observed among GlycA, IDP-1444, and tissue-specific transcriptomic regulation for brain frontal cortex and testis (rs12048743—chr1q32.1; posterior probability > 0.8). While we also tested causality between PTSD, metabolomic biomarkers, and brain IDPs, these were not consistent across different genetically informed causal inference methods.

CONCLUSIONS: Our findings highlight a new putative pleiotropic mechanism that links systemic inflammation and pallidum structure to PTSD.

https://doi.org/10.1016/j.bpsgos.2025.100482

Posttraumatic stress disorder (PTSD) develops in a subset of individuals who witness or experience severe stress or trauma (1). Its pathogenesis is directly related to the interplay between the environment and biological characteristics (2). While environmental risk factors for PTSD are well documented (3–7), the biological mechanisms involved remain largely unclear. Genome-wide association studies (GWASs) have identified several genetic risk loci for PTSD and revealed the involvement of molecular pathways, such as pathways related to stress response and the immune system (8). In addition to genetic associations, PTSD has been linked to changes related to other molecular domains, including transcriptomics (9) and proteomics (10). Circulating biomarkers, especially lipids and inflammatory biomarkers, have been investigated with respect to PTSD, highlighting the potential role of lipid and inflammatory biomarkers in PTSD pathophysiology (11–14). Recently, genetically informed studies uncovered pleiotropic mechanisms (i.e., shared genetic effects) that link PTSD to metabolic conditions and lipids (e.g., metabolic syndrome), inflammatory biomarkers (e.g., C-reactive protein [CRP], interleukin [IL] 6 and IL-1β, tumor necrosis factor α and interferon gamma), as well as other blood biomarkers (15–20).

Beyond blood-based analyses, brain imaging studies have shed light on PTSD pathophysiology, showing the potential role of structural and functional changes in specific brain regions. Particularly, PTSD has been associated with reduced hippocampal and amygdala volume (21) and cortical thickness in the prefrontal, insular, and cingulate cortices (22,23). Notably, PTSD has been linked to brain regions involved in emotional regulation and processing of sensory information (24). In addition to brain structures defined by anatomical boundaries, structural covariance networks in PTSD have revealed widespread reduced cortical thickness (24).

ISSN: 2667-1743

While understanding the blood-brain interplay has important translational implications for PTSD, to our knowledge, the relationship among PTSD, blood biomarkers, and brain imaging-derived phenotypes (IDPs) remains unexplored. By investigating PTSD pleiotropic relationships on metabolome-wide and brainwide scales, we deepened the understanding of PTSD etiology by uncovering a novel mechanism that links inflammation and pallidum structure.

METHODS AND MATERIALS

To investigate the pleiotropy (i.e., genetic variants associated with multiple traits) between PTSD, brain imaging phenotypes, and circulating biomarkers, we leveraged genome-wide, brain-wide, and metabolome-wide datasets available from multiple cohorts (Figure 1). Applying a hypothesis-generating study design to these large-scale datasets, we aimed to uncover new insights into the genetic mechanisms that link PTSD to blood metabolome and brain structure and function. Due to the lack of data representative of other population groups, only information from individuals of European ancestry (EUR) was investigated. The study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (REK 467496).

Datasets

Posttraumatic Stress Disorder. PTSD GWAS Freeze 3 data were obtained from the Psychiatric Genomics Consortium (PGC) PTSD working group. These data were generated from a GWAS meta-analysis that combined information from 1,222,882 EUR individuals (137,136 cases) assessed in 88 cohorts (e.g., the UK Biobank [UKB], Million Veteran Program, FinnGen, Army STARRS, and Estonian Biobank) (8). Depending on the design of the samples combined, PTSD status was derived from clinician-administered or self-reported instruments, the PTSD Checklist for DSM-IV, or electronic health records. The PGC-PTSD GWAS can be considered an extremely powerful dataset for pleiotropy-focused analyses because it has identified 95 genome-wide significant loci and showed a single nucleotide polymorphism–based heritability (h^2_{SNP}) z score of 26.6.

To assess the specificity of our PTSD results, we also investigated anxiety, depression, and possible third-variable phenotypes. The anxiety GWAS included 1,096,458 EUR individuals (25). The depression GWAS included 1,999,601 EUR individuals (26). Similarly to the PTSD GWAS (8), depression and anxiety GWASs were generated from the meta-analyses of

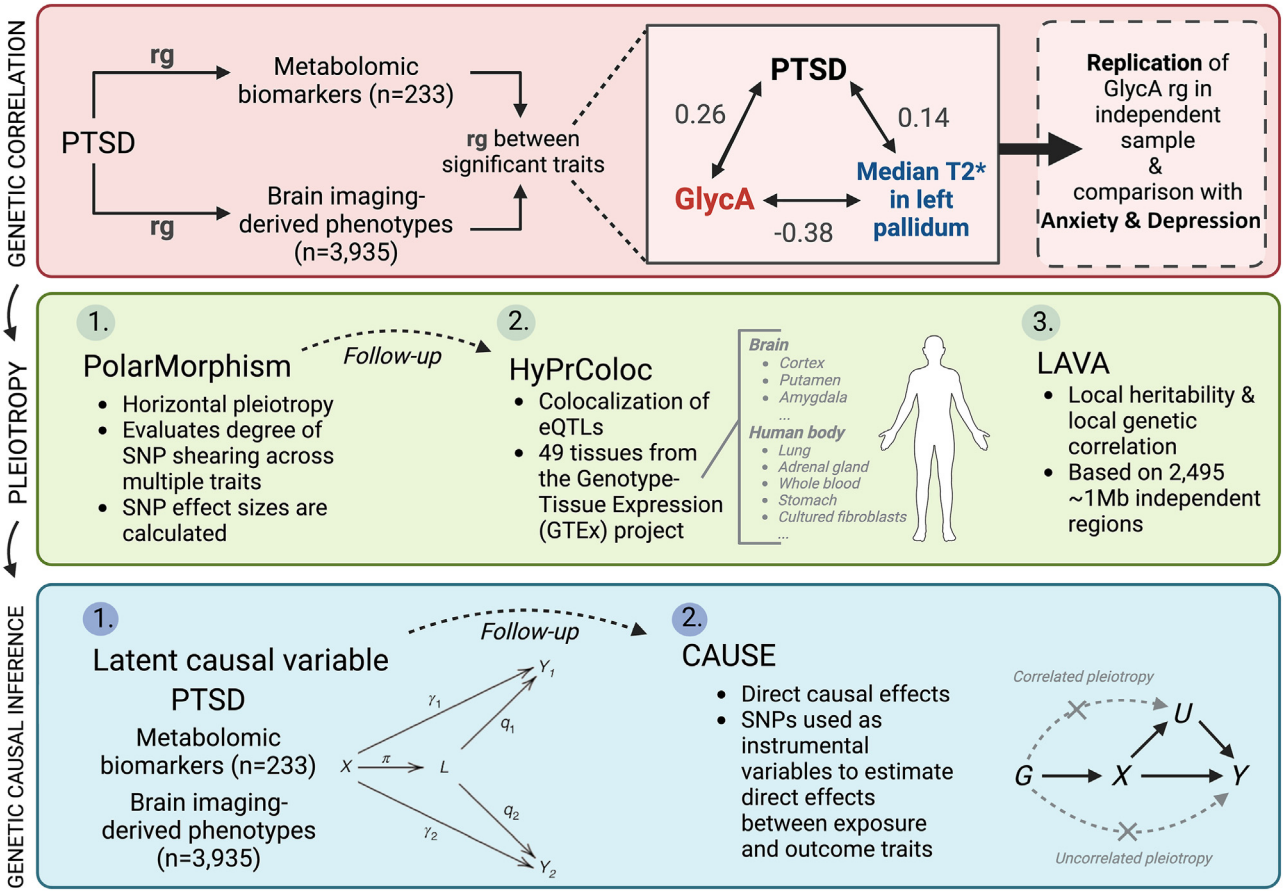

Figure 1. Study overview. (We acknowledge BioRender.com for providing the web interface for creating Figure 1.) CAUSE, causal analysis using summary effect estimates; eQTL, expression quantitative trait locus; GlycA, glycoprotein acetyls; HyPrColoc, hypothesis prioritization for multiple trait colocalization; LAVA, local analysis of (co)variant association; PTSD, posttraumatic stress disorder; SNP, single nucleotide polymorphism.

cohorts assessed with different instruments and using different scales (25,26). As possible third variables, we considered insomnia (GWAS EUR n = 386,988) (27), alcohol drinks per week (GWAS n = 666,978) (28), cigarettes per day (GWAS EUR n = 326,497) (28), and physical activity (GWAS EUR n = 606,891) (29).

Metabolomic Data. To assess blood metabolome, we leveraged data generated from a previous GWAS meta-analysis conducted on up to 136,016 EUR individuals (30). This sample included participants enrolled from 27 cohorts (not including the UKB) with different characteristics and using different sample types (serum, plasma, fasted, and nonfasted). Most of them were general population samples not enriched for any particular condition. This previous GWAS investigated 233 metabolomic traits, including blood biomarkers related to lipids, inflammation, fluid balance, amino acids, ketones, and glycolysis/gluconeogenesis (30). Metabolic biomarkers were primarily quantified in plasma using nuclear magnetic resonance (NMR) spectroscopy (30). To replicate the findings observed in this blood metabolome GWAS, we also analyzed data from an independent blood metabolome GWAS conducted with up to 115,082 UKB participants (31). In this sample, metabolomic traits were measured from nonfasting EDTA plasma samples. The NMR analyses were conducted in a random subsample of the UKB cohort. The high-throughput NMR platform from Nightingale Health was used for both discovery and replication metabolome datasets.

Brain IDPs. Information regarding 3935 brain IDPs was derived from a GWAS conducted on up to 33,224 UKB participants (32). UKB protocols for brain imaging acquisition, data preprocessing, and analysis techniques generated brain IDPs from 6 magnetic resonance imaging (MRI) modalities: T1-weighted structural imaging, T2-weighted fluid-attenuated inversion recovery imaging, diffusion-weighted imaging, susceptibility-weighted imaging, resting-state functional MRI (rs-fMRI), and task-based fMRI (32). A detailed description of the sample, data processing, and quality control is available elsewhere (32–34).

Sample Overlap. The genome-wide association statistics analyzed were generated from samples that overlapped in some cases. For example, the UKB cohort was included in all GWASs analyzed except for the discovery metabolome GWAS. To avoid biases due to sample overlap, we applied methods that were specifically designed to analyze genome-wide association statistics accounting for sample overlap among the cohorts being investigated.

Global and Local Genetic Correlation

PTSD global genetic correlation (r_g; i.e., the correlation of genetic effects between different traits across the genome) was calculated with respect to metabolomic biomarkers and brain IDPs using the linkage disequilibrium score regression (LDSC) method (35). LD scores were precomputed from the 1000 Genomes Project (phase 3 EUR population) (36), considering SNPs included in the HapMap3 reference panel (37). Consistent with LDSC recommendations, only traits with an h^2_{SNP} z score > 4 were considered (35). A Bonferroni correction was applied to account for the number of traits tested within metabolome (n = 153) and brain imaging domains (n = 2511) in PTSD genetic correlation analyses.

In addition to global genetic correlation, we estimated PTSD-metabolome-brain local genetic correlations (i.e., the correlation of genetic effects between different traits across genetic variants in a local region) using the local analysis of (co) variant association (LAVA) method (38). This method allowed us to simultaneously analyze local genetic correlations across multiple phenotypes (38). We used the 1000 Genomes Project phase 3 EUR populations (36) as the LD reference and GRCh37 as the reference genome. To account for sample overlap, LAVA estimates were adjusted for the intercept from bivariate LDSC (38). Local genetic correlations (rho) were calculated for 2495 partially independent ~1 Mb genetic regions.

Horizontal Pleiotropy

To assess genetic loci that may contribute to horizontal pleiotropy (i.e., genetic variants affecting multiple traits through independent biological pathways) between significantly associated traits, we leveraged the PolarMorphism package (39). This tool allowed us to evaluate horizontal pleiotropy across multiple traits, attenuating the effect of vertical pleiotropy (i.e., genetic variants affecting multiple traits due to cause-effect relationships among the latter) observed in the genetic correlation via a decorrelating transformation. By transforming SNP effect sizes to polar coordinates, we were able to quantify the SNP effect (r) and the degree of SNP sharing between traits (theta) (39). As recommended by PolarMorphism developers (39), a theta false discovery rate (FDR) $q < .05$ was applied for multiple testing correction to account for the correlation among the variants tested due to LD.

Colocalization Analysis

Pleiotropic variants were further examined using hypothesis prioritization for multiple trait colocalization (HyPrColoc) (40). This method applies Bayesian inference to detect genetic associations between complex traits within specific gene regions (40). By integrating this information with disease-associated traits, the method assesses whether pleiotropy within a certain genomic region is due to shared causal loci (i.e., colocalization). Using HyPrColoc, we evaluated whether variants with evidence of brain-metabolome pleiotropy colocalized with tissue-specific transcriptomic regulation. Information regarding tissue-specific expression quantitative trait loci (eQTLs) was obtained from GTEx version 8 (41) for all 48 available tissues. Consistent with the threshold used in the original HyPrColoc study (40), a posterior probability >70% was considered to be evidence of colocalization.

Genetically Informed Causal Inference

Potential causal effects linking PTSD to metabolomic traits and brain IDPs were assessed through a latent causal variable (LCV) analysis (42). Under the assumption of a single effect-size distribution, LCV estimates the genetic causality proportion (gcp) as a measure of how a latent variable can explain the genetic correlation between 2 traits (42). Positive gcp can

range from 0 to 1 and reflect the causal effect between phenotype 1 (PTSD in the current study) and phenotype 2 (metabolomic trait or brain IDP in the current study). Conversely, negative gcp values indicate a causal relationship between phenotype 2 and phenotype 1. The sign of the rho statistics indicates the sign of the genetic correlation between the phenotypes being tested. If rho $>$ 0, phenotypes 1 and 2 are positively genetically correlated, while if rho $<$ 0, phenotypes 1 and 2 are negatively correlated. As recommended (42), significant results after multiple testing correction were classified as evidence of genetic causality considering $|gcp| > 0.6$.

To follow up on LCV analysis results, we performed a causal analysis using summary effect estimate (CAUSE) (43). These methods are based on different assumptions, and effects consistent between them are less likely to be biased by violations of the assumptions that underlie each model. While the LCV approach assesses a latent variable that underlies the global genetic correlation observed between 2 traits, the CAUSE approach estimates direct causal effects using genetic variants as instrumental variables that account for horizontal pleiotropy (43) using a Mendelian randomization (MR) framework. CAUSE parameters were estimated based on a random subset of 1 million variants for brain IDPs and 650,000 variants for metabolomic biomarkers, and the following parameters were set for LD pruning steps in PLINK version 1.9 (44): –clump-kb 10,000, –clump-p1 0.001, and –clump-r2 0.01. Statistical significance was evaluated by comparing the expected log pointwise posterior density of null, sharing, and causal models through a z test.

RESULTS

Genetic Correlation

We analyzed PTSD global genetic correlations with respect to metabolomic biomarkers and brain IDPs. After Bonferroni correction that accounted for the number of metabolomic traits tested (n = 153, $p < 3.27 \times 10^{-4}$) (Table S1), PTSD was genetically correlated with 1 metabolomic biomarker, namely glycoprotein acetylation (GlycA) (r_g = 0.26, SE = 0.069, $p = 1.00 \times 10^{-4}$). Two significant genetic correlations were also observed for PTSD after Bonferroni correction that accounted for the number of brain IDPs (n = 2511, $p < 1.99 \times 10^{-5}$) (Table S2): IDP-590 (volume of G-Ins-lg+S-cent-ins in the right hemisphere, r_g = 0.18, SE = 0.036, $p = 4.10 \times 10^{-7}$) and IDP-1444 (median T2* in left pallidum, r_g = 0.14, SE = 0.032, $p = 1.39 \times 10^{-5}$). Interestingly, GlycA was also genetically correlated with IDP-1444 ($r_g = -0.38$, SE = 0.13, $p = 2.50 \times 10^{-3}$) but not with IDP-590 ($r_g = -0.095$, SE = 0.12, p = .43). Considering an independent blood metabolome GWAS (31), the genetic correlation between PTSD and GlycA (r_g = 0.23, SE = 0.026, $p = 5.99 \times 10^{-19}$) was replicated, while IDP-1444 and GlycA showed a nominal genetic correlation (r_g = 0.099, SE = 0.040, p = .0124) in a direction opposite to the one observed in the discovery cohort.

To assess the specificity of these genetic correlations, we also investigated anxiety and depression, 2 traits highly comorbid with PTSD (45). Leveraging an anxiety GWAS including 1,096,458 EUR individuals (25), anxiety showed no genetic correlation with GlycA (r_g = 0.072, SE = 0.074, p = .331). Similarly, leveraging a depression GWAS that includes up to 1,999,601 EUR individuals (26), depression showed only a nominally significant genetic correlation with GlycA (r_g = 0.138, SE = 0.064, p = .032), with an estimate that was about half of the one observed for PTSD. Anxiety and depression were both genetically correlated with IDP-1444 (anxiety r_g = 0.14, SE = 0.033, $p = 3.52 \times 10^{-5}$; depression r_g = 0.17, SE = 0.031, $p = 3 \times 10^{-8}$). Considering possible third variables, GlycA was nominally genetically correlated with insomnia (r_g = 0.20, SE = 0.065, p = .019) and cigarettes per day (r_g = 0.16, SE = 0.065, p = .013), while none of the selected phenotypes was genetically correlated with IDP-1444 (Table S3).

In addition to global genetic correlations, we observed multiple local genetic correlations between PTSD, GlycA, and IDP-1444 that survived Bonferroni correction that accounted for the number of genetic regions tested (n = 2495, $p < 2.00 \times 10^{-5}$) (Table S4). While none of them were shared across the 3 traits of interest, 7 of the chromosomal regions showed local genetic correlations between PTSD and GlycA, and 1 region showed correlations between PTSD and IDP-1444 (Table 1). Consistent with the direction of global genetic correlations, all local genetic correlations were positive except for 1 negative association between PTSD and GlycA in chromosomal region 3:4,835,084-5,496,182 (rho = −0.98, $p = 5.55 \times 10^{-6}$). In this region, 22 genome-wide significant associations were reported by the GWAS catalog (46), with the strongest ones being related to gamma-glutamyl transferase and alkaline phosphatase (Table S5). Five of the 7 PTSD-GlycA local genetic correlations were within the major histocompatibility complex (MHC) region, with many immune-related genome-wide significant associations being identified in these loci (Tables S6–S10). The other PTSD-GlycA local genetic correlation located outside the MHC region was on chromosome 15 (hg38 coordinates 96,975,279–98,136,684). In this region, many genome-wide significant associations were related to brain morphology (e.g., hippocampal volume, subiculum volume, and vertex-wise sulcal depth) (Table S11). The local genetic correlation between PTSD and IDP-1444 was located on chromosome 19 (hg38 coordinates 4,751,819–5,488,784), where genome-wide significant associations included different domains such as height, mouth ulcers, neutrophil percentage of white cells, smoking initiation, and hypothyroidism (Table S12). No local genetic correlation between GlycA and IDP-1444 survived Bonferroni multiple testing correction (Table S4).

Horizontal Pleiotropy

To further investigate the global genetic correlations that we observed, we investigated the horizontal pleiotropy among PTSD, IDP-1444, and GlycA using the PolarMorphism package (39). While we did not observe single variants with evidence of horizontal pleiotropy among the 3 phenotypes of interest (Table S13), 2 variants were statistically significant after FDR multiple testing correction for horizontal pleiotropy between IDP-1444 and GlycA (Figure 2; Tables S13 and S14): rs12048743 ($z_{IDP\text{-}1444} = 17.14$, $z_{GlycA} = -6.07$, $r = 2.01 \times 10^{-71}$, theta $p = 2.06 \times 10^{-8}$, theta $q = 1.23 \times 10^{-5}$) and rs10157145 ($z_{IDP\text{-}1444} = 9.43$, $z_{GlycA} = -5.68$, $r = 4.75 \times 10^{-2}$, theta $p = 1.40 \times 10^{-6}$, theta $q = 4.18 \times 10^{-4}$). These SNPs are localized within the same genetic region in chromosome 1 and in LD in

Table 1. Posttraumatic Stress Disorder Local Genetic Correlations That Survived Bonferroni Multiple Testing Correction ($p < 2 \times 10^{-5}$)

Chromosomal Region (hg38)	Phenotype	Rho	*p*	No. of GWS Associations
6:31,361,461–31,431,172	GlycA	0.88	3.10×10^{-8}	448
6:31,538,210–32,319,901		0.73	3.42×10^{-7}	2130
6:32,319,902–32,565,577		0.74	1.51×10^{-6}	1115
6:31,217,494–31,361,556		0.69	2.24×10^{-6}	1142
3:4,845,184–5,506,282		−0.98	5.55×10^{-6}	22
15:96,975,279–98,136,684		0.85	7.43×10^{-6}	65
6:30,826,007–31,217,493		0.67	9.64×10^{-6}	732
19:4,751,819–5,488,784	IDP-1444	0.54	3.87×10^{-6}	156

GlycA, glycoprotein acetyls; GWS, genome-wide significant; IDP, imaging-derived phenotype.

EUR populations (LD $r^2 = 0.68$). To understand the regulatory mechanisms that underlie this region, we conducted a multitrait localization analysis considering ±1 Mb surrounding these variants (GRCh37 chromosome 1:204,108,163–206,261,742). While there was no colocalization with the eQTLs of a specific gene, we observed 4 tissues with evidence of regional colocalization (regional posterior probability > 0.7) between GlycA and tissue-specific transcriptomic regulation and between GlycA and IDP-1444 (Table S15): brain cortex, brain frontal cortex (Brodmann area 9), caudate (basal ganglia), and testis. IDP-1444 also showed regional colocalization with the nucleus accumbens (basal ganglia; posterior probability = 0.97). Conversely, regional colocalization between GlycA and transcriptomic regulation was observed for all other tissues (posterior probability > 0.7) except putamen (basal ganglia), nucleus accumbens (basal ganglia), and subcutaneous adipose tissue (Table S15).

Genetically Informed Causal Inference

LCV analysis was performed to investigate genetically inferred effects linking PTSD, metabolomic biomarkers, and IDPs. As mentioned in Methods and Materials, positive and negative gcp values reflect the direction of the putative causal effect (i.e., PTSD→phenotype and phenotype→PTSD, respectively) while the sign of the effect is given by the rho statistics. After Bonferroni correction that accounted for the number of metabolomic traits tested ($n = 153$, $p < 3.27 \times 10^{-4}$, $|gcp| > 0.6$) (Table S16), PTSD appeared to be affected by 2 metabolomic biomarkers: triglycerides to total lipids ratio in very low-density lipoprotein (VLDL) (gcp = −0.75, $p = 1.91 \times 10^{-11}$, rho = 0.22) and cholesteryl esters to total lipids ratio in intermediate-density lipoprotein (IDL) (gcp = −0.69, $p = 2.02 \times 10^{-7}$, rho = −0.26). The effect of PTSD on GlycA was not statistically significant (gcp = 0.55, $p = .079$, rho = 0.33). We also observed 3 significant genetically inferred causal effects after Bonferroni correction accounting for the number of brain IDPs ($n = 2511$, $p < 1.99 \times 10^{-5}$, $|gcp| > 0.6$) (Table S17). These showed all negative gcp statistics, highlighting the effect of brain structure and function on PTSD. All the Bonferroni-significant gcp estimates were related to rs-fMRI connectivity patterns (Table S17). This included independent component analysis-100 components (ICA-100) edge 363 (gcp = −0.68, $p = 1.65 \times 10^{-26}$, rho = 0.13), ICA-100 edge 809 (gcp = −0.66, $p = 1.09 \times 10^{-11}$, rho = −0.18), and ICA-100

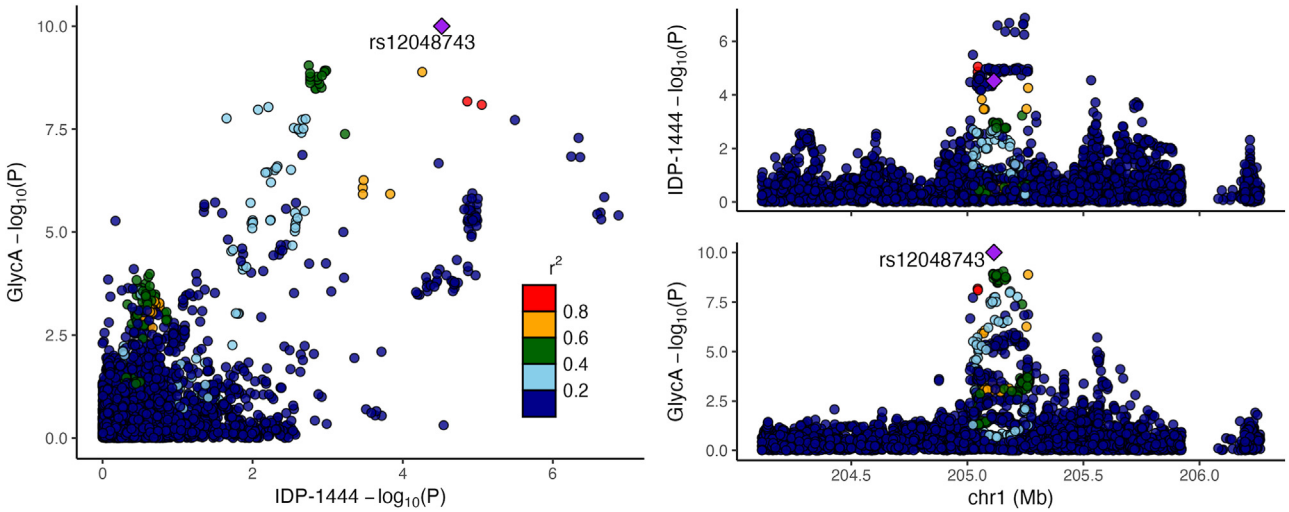

Figure 2. Regional plot of rs12048743 horizontal pleiotropy between GlycA and IDP-1444. chr, chromosome; GlycA, glycoprotein acetyls; IDP, imaging-derived phenotype.

edge 1173 (gcp = −0.63, $p = 2.15 \times 10^{-22}$, rho = 0.11). With respect to IDP-1444, a suggestive effect on PTSD was observed (gcp = −0.46, $p = .008$, rho = 0.15). While LCV identified multiple genetically inferred causal effects, none of these were confirmed by the CAUSE method (Tables S18 and S19).

DISCUSSION

PTSD is a psychiatric disorder that is often accompanied by mental and somatic comorbidities (47), leading to a reduced quality of life and health expectancy (48,49). While previous research linked PTSD to both brain imaging and blood markers, investigating the brain-blood interplay in PTSD could help increase understanding of the PTSD pathogenesis more comprehensively. In the current study, we leveraged genome-wide information to integrate brain IDPs derived from 6 MRI modalities and metabolomic biomarkers derived from NMR spectroscopy. Applying multiple analytic approaches (Figure 1), we explored how different pleiotropic mechanisms contribute to brain-metabolome pleiotropy in the context of PTSD. As previously hypothesized (2), while the brain is surely the key organ linked to PTSD pathogenesis, pathways (e.g., inflammation) that affect peripheral tissues likely contribute to the disease. Because of the complexity of biological systems, understanding how brain and other organs are related to PTSD requires a multiperspective design. Accordingly, leveraging genome-wide information, we tested different hypotheses: 1) PTSD-brain-metabolome shared genetic effects across the genome and within specific regions; 2) impact of PTSD-brain-metabolome on tissue-specific transcriptomic regulation; and 3) possible cause-effect relationships contribute to the associations among PTSD, blood metabolome, and brain IDPs.

Our primary finding was related to the potential genetic relationships among PTSD, GlycA, and median T2* in the left pallidum. However, while PTSD-GlycA genetic correlation was replicated in an independent cohort, GlycA pleiotropy with pallidum structure was not consistent across the discovery and replication cohorts. This may be due to the characteristics of the cohorts investigated. The discovery dataset was generated from a meta-analysis that included diverse cohorts (30), while the replication dataset was based on the UKB cohort (31). With respect to technical differences, both metabolomic datasets were generated from NMR spectroscopy, but discovery meta-analysis included different sample types (serum, plasma, fasted, and nonfasted) while the UKB analysis was performed using nonfasted plasma samples. These differences did not affect the PTSD-GlycA pleiotropy likely due to the fact that the estimates observed were highly statistically significant. Conversely, although it survived multiple testing correction, the genetic correlation between GlycA and IDP-1444 was less statistically strong than the one observed between PTSD and GlycA. This might also have contributed to the failed replication. With respect to the genetic correlation estimates that we observed between metabolomic traits and brain IDPs, they are within the range observed in previous studies (50–52), and this reflects the extent of the pleiotropy among these distinct biological systems.

GlycA is a marker of systemic inflammation and has been associated with mortality (53). It appears to be more stable than high-sensitivity CRP as a marker of chronic inflammation (54). PTSD-GlycA pleiotropy supports the role of inflammation in PTSD pathogenesis. A systematic review, meta-analysis, and metaregression of observational studies confirmed the associations between inflammatory biomarkers and PTSD (11). The relationship between PTSD and inflammation has also been supported by multiple genetically informed studies (16,20,55). However, to our knowledge, no study formally investigated GlycA in the context of PTSD. A GlycA polygenic risk score based on a subset of our discovery cohort has been associated with avoidance of activities/situations related to previous stressful events (19). A previous MR study did not find strong evidence of causal effects linking GlycA (derived from UKB metabolome GWAS) and depression symptoms (56). In addition to genetically informed studies, observational metabolomic studies using the Nightingale Health NMR platform also found associations between GlycA and mental health outcomes. Similarly, GlycA has been associated with adverse experiences in children (57–59) and internalizing problems in infants (60). Previous investigations have linked GlycA to depression in the general population (61–63) and during pregnancy (64) and to overall mental health in children and midlife adults (65). Consistent with our analysis, observational studies have not observed any relationship between GlycA and anxiety (66). With respect to other brain-related outcomes, GlycA has been associated with cognition (67), insomnia symptoms (68), Alzheimer's disease (69), and neurodevelopmental delay (70). Consistent with its potential impact on brain structure, GlycA has also been linked to white matter hyperintensities (71).

Our analyses support the idea that the global genetic correlation between PTSD and GlycA is due to shared genetic effects rather than cause-effect relationships. In particular, we uncovered evidence of local genetic correlation between these 2 traits in several genetic regions. Five of the 7 PTSD-GlycA local genetic correlations were within the MHC region, which is densely packed with genes involved in immune response and inflammation (e.g., *TNF*, *LTA*, *NFKBIL1*, *C2*, *C4B*, *CFB*, *AGER*, *HLA-DRA*, *HLA-DRB*, *HLA-DRB5*, *HLA-DRB6*, *TSBP1*, *TSBP1-AS1*, *BTNL2*, *PSORS1C1*, *PSORS1C2*). This supports further previous hypotheses regarding the role of the immune system and inflammation in PTSD pathogenesis (72–75). On chromosome 15, another region (position 96,975,279–98,136,684) with evidence of PTSD-GlycA pleiotropy was identified by previous GWASs of brain morphology phenotypes (76,77). While *ARRDC4* is the only protein-coding gene in this region, and its function is poorly understood, many candidate cis-regulatory elements exist such as distal and proximal enhancers, promoters, and CTCF sites. This supports that GlycA-PTSD pleiotropy in this region may be mediated by regulations that affect one or more genes located at variable distances. While the local genetic correlation observed in these regions was consistent with the global positive genetic correlation observed between PTSD and GlycA, we also identified a region (chromosome 3: 4,845,184–5,506,282) with an inverse genetic correlation between these traits. Here, there are several genes involved in immune response (*EDEM1*) (78), neuronal function (*ITPR1*) (79), and inflammation (*BHLHE40*) (80), and previous GWASs identified strong associations with blood biomarkers such as gamma-glutamyl transferase (81) and serum alkaline

phosphatase (82). The inverse PTSD-GlycA pleiotropy observed in this region may result from complex interactions among different regulatory pathways.

GlycA and PTSD were both genetically correlated with median T2* in the left pallidum (IDP-1444). This brain region is involved in adaptive behaviors (83) and proprioceptive movement (84). Multiple imaging studies have reported associations of PTSD with pallidum structure and function (85–94). In particular, the left pallidum showed associations 1) between gray matter volume and response to severe stress (95), 2) increased neural activity and emotional empathy in PTSD cases (93), and 3) altered structural connectivity and dissociative PTSD (85). The left pallidum was also one of the brain areas most prominently involved in correct PTSD classification using fMRI (94). In our study, a local genetic correlation between PTSD and IDP-1444 was present in a region that had previously been associated with different health domains, such as smoking initiation (28) and hypothyroidism (96). Here, there are genes involved in epigenetic regulation (*UHRF1* and *KDM4B*) (97,98), neuroinflammation (*TICAM1*) (99), and lipid metabolism (*PLIN3*) (100,101). These molecular pathways are considered among the possible contributors that link brain function to PTSD pathogenesis (102–104).

We also identified a locus (index variant rs12048743) with evidence of horizontal pleiotropy between GlycA and IDP-1444. Integrating tissue-specific transcriptomic regulation, we observed regional colocalization with respect to the brain cortex and testis. This suggests that the shared genetic mechanisms are also linked to both brain and peripheral regulatory mechanisms. GlycA genetic effects colocalized with most tissues available in this region, highlighting potential cross-tissue regulatory mechanisms. Conversely, IDP-1444 showed genetic colocalization with the nucleus accumbens, which is consistent with the fact that they are the primary components of the basal ganglia network (105).

Our LCV analyses highlighted 2 lipid-related metabolites (triglycerides to total lipids ratio in very large VLDL and cholesteryl esters to total lipids ratio in IDL) that affect PTSD. A possible effect of lipid-related metabolites was reported in a previous MR analysis that investigated emotional and behavioral responses to traumatic stress (19). However, LCV results were not confirmed by a subsequent CAUSE analysis. These conflicting results may be due to differences in the statistical power between the 2 methods or the inadequate modeling of these causal effects by one of the 2 approaches. The same inconsistency was also present when testing brain IDPs. While the LCV approach identified 3 brain IDPs that may affect PTSD, none of these were replicated by the CAUSE method. Nevertheless, the effect direction of the LCV results (brain IDP→PTSD) is consistent with the direction observed in a brainwide MR analysis of anxiety disorders and symptoms (brain IDP→anxiety) (106).

Our study has several limitations. Due to the lack of representation of diverse populations in large-scale GWASs, the analysis was limited to genetic information available from EUR individuals. Therefore, our results cannot be generalized to other populations. Our metabolome-wide dataset does not adequately represent inflammation-related biomarkers, and therefore GlycA effects may be shared among inflammatory metabolites. The inconsistent results in our genetically informed analyses highlight the complexity of investigating PTSD cause-effect relationships and the need to use multiple approaches to assess the generalizability of findings across methods based on different assumptions. Last, while insomnia, alcohol drinking, tobacco smoking, and physical activity did not show the same genetic correlation patterns of PTSD with GlycA and IDP-1444, other phenotypes may contribute to the pleiotropic relationships that we observed in our study.

Conclusions

Our study highlights that pleiotropic mechanisms between brain IDPs and blood metabolome can contribute to the genetic liability to PTSD. In particular, our findings point toward the potential interplay between systemic inflammation and pallidum structure due to shared genetic effects that also appear to act on brain-specific transcriptomic regulation. These support the possibility of targeting systemic inflammation to intervene in brain-related pathogenetic pathways involved in PTSD pathogenesis. In this context, future studies will also need to explore how exposure to traumatic events can play a role in the interplay among PTSD, systemic inflammation, and changes in brain structure and function.

ACKNOWLEDGMENTS AND DISCLOSURES

SL is supported by an International Training Grant and Ph.D. scholarship from the University of Bergen. RP is supported by grants from the National Institutes of Health (Grant Nos. RF1MH132337 and R33DA047527) and a grant from One Mind. MT is supported by the Research Council of Norway (Grant Nos. 273291 and 273446).

We thank all participants of the included cohorts, as well as investigators of previous articles for making the GWAS summary statistics available.

SL and RP were responsible for concept and study design. EF was responsible for data acquisition. SL, MT, BC-M, and KS were responsible for analysis. SL and RP were responsible for writing the original draft of the article. All authors were responsible for interpretation of data. All authors were responsible for and approved the final version of the article.

Metabolomics GWAS summary statistics are available from https://www.ebi.ac.uk/gwas/publications/38448586. GlycA GWAS summary statistics used for replication analysis are available from https://www.ebi.ac.uk/gwas/studies/GCST90092821. GWAS summary statistics for brain IDPs are available from https://open.win.ox.ac.uk/ukbiobank/big40/. Tissues from the GTEx portal are available from https://gtexportal.org/. Code for LDSC is available from https://github.com/bulik/ldsc. Code for LCV analysis is available from https://github.com/lukejoconnor/LCV.

RP received a research grant from Alkermes outside the scope of the current study and received an honorarium for his editorial work for the scientific journal *Complex Psychiatry*. All other authors report no biomedical financial interests or potential conflicts of interest.

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Received Jan 17, 2025; revised Feb 16, 2025; accepted Mar 1, 2025.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsgos.2025.100482.

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