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Altered gene expression and PTSD symptom dimensions in World Trade Center responders

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Despite experiencing a significant trauma, only a subset of World Trade Center (WTC) rescue and recovery workers developed posttraumatic stress disorder (PTSD). Identification of biomarkers is critical to the development of targeted interventions for treating disaster responders and potentially preventing the development of PTSD in this population. Analysis of gene expression from these individuals can help in identifying biomarkers of PTSD. We established a well-phenotyped sample of 371 WTC responders, recruited from a longitudinal WTC responder cohort using stratified random sampling, by obtaining blood, self-reported and clinical interview data. Using bulk RNA-sequencing from whole blood, we examined the association between gene expression and WTC-related PTSD symptom severity on (i) highest lifetime Clinician-Administered PTSD Scale (CAPS) score, (ii) past-month CAPS score, and (iii) PTSD symptom dimensions using a 5-factor model of re-experiencing, avoidance, emotional numbing, dysphoric arousal and anxious arousal symptoms. We corrected for sex, age, genotype-derived principal components and surrogate variables. Finally, we performed a meta-analysis with existing PTSD studies (total $N = 1016$), using case/control status as the predictor and correcting for these variables. We identified 66 genes significantly associated with total highest lifetime CAPS score (FDR-corrected $p < 0.05$), and 31 genes associated with total past-month CAPS score. Our more granular analyses of PTSD symptom dimensions identified additional genes that did not reach statistical significance in our analyses with total CAPS scores. In particular, we identified 82 genes significantly associated with lifetime anxious arousal symptoms. Several genes significantly associated with multiple PTSD symptom dimensions and total lifetime CAPS score (*SERPINA1, RPS6KA1*, and *STAT3*) have been previously associated with PTSD. Geneset enrichment of these findings has identified pathways significant in metabolism, immune signaling, other psychiatric disorders, neurological signaling, and cellular structure. Our meta-analysis revealed 10 genes that reached genome-wide significance, all of which were downregulated in cases compared to controls (*CIRBP, TMSB10, FCGRT, CLIC1, RPS6KB2, HNRNPUL1, ALDOA, NACA, ZNF429 and COPE*). Additionally, cellular deconvolution highlighted an enrichment in CD4 T cells and eosinophils in responders with PTSD compared to controls. The distinction in significant genes between total lifetime CAPS score and the anxious arousal symptom dimension of PTSD highlights a potential biological difference in the mechanism underlying the heterogeneity of the PTSD phenotype. Future studies should be clear about methods used to analyze PTSD status, as phenotypes based on PTSD symptom dimensions may yield different gene sets than combined CAPS score analysis. Potential biomarkers implicated from our meta-analysis may help improve therapeutic target development for PTSD.

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is a complex psychiatric disorder that can develop after experiencing a traumatic event. The attacks on the World Trade Center (WTC) on September 11, 2001 and their aftermath had a substantial impact on the physical and mental health of WTC rescue, recovery and clean-up workers, but only a subset developed PTSD. These differing clinical outcomes after experiencing trauma imply a role for biological and genetic influence in PTSD. Our cohort provides an unprecedented opportunity into PTSD insights, because participants have been deeply phenotyped for a shared, specific trauma. This is also the largest study to have tested gene expression associations with clinician-validated PTSD measures.

Understanding the biological mechanisms underlying PTSD will require careful dissection and analysis of many constituent symptoms and risk factors. PTSD is uniquely heterogeneous among psychiatric disorders, with complex and detailed diagnostic criteria that allow for 636,120 different combinations of symptoms [1]. Additional heterogeneity in PTSD stems from the type and extent of trauma. It has been well established that PTSD is a heterogenous disorder and that trauma type plays a role in differential outcomes. In the field of WTC-related trauma exposures, some work has already been done to elucidate gene expression and clinical outcomes [2–8]. Further, work by our group and others has demonstrated differential genetic heritability of PTSD according to trauma type [9, 10].

To examine PTSD symptom dimensions, we employed the five-factor 'dysphoric arousal' model of PTSD symptoms [11], which consists of separate clusters of re-experiencing, avoidance, emotional numbing, dysphoric arousal (i.e., sleep difficulties, concentration problems, anger/irritability), and anxious arousal (i.e., hypervigilance, exaggerated startle response) symptoms; our group has previously found that this more nuanced model of DSM-IV PTSD symptoms provides optimal fit to characterizing the dimensional structure of WTC-related PTSD symptoms in more than 10,000 WTC responders [11]. To our knowledge, we are the first study to examine gene expression associations with this five-factor model. The distribution of our phenotypes is purposefully non-normalized in order to maximize the residual variance of each phenotype. For differential gene expression, other studies have demonstrated the benefit of non-normalized data in interpreting genetic differences [12, 13].

Identification of biomarkers will be critical to the development of targeted interventions for treating disaster responders and potentially preventing the development of PTSD in this population. Gene expression analysis from WTC responders is uniquely useful to deduce the biological heterogeneity in PTSD, given their exposure to a similar and well-documented trauma. Our study is the first to test whole blood-derived biomarkers in a meta-analysis with other gene expression studies. Data on WTC-related traumatic exposures of responders analyzed here, in combination with their heterogenic clinical outcomes, makes this a critical study to understand PTSD development and chronicity after shared traumatic events. Although candidate gene expression and methylation studies have explored genes involved in canonical stress signaling pathways in PTSD, regulated by the hypothalamus-pituitary-adrenal (HPA) axis, and immune and sympathetic nervous systems, few have been able to control for length of time since exposure, nor so specifically delineate trauma type and secondary exposures such as dust cloud exposure severity. While the WTC-related exposures experienced by rescue, recovery and clean-up workers in this cohort ranged in severity, the traumatic event –encompassing the 9/11 attacks and their aftermath– happened in a discrete, specific time window. Further, this sample is highly phenotyped with in-person clinical psychiatric evaluations, also including medical examination and laboratory testing.

The existence of this cohort and the generous participation of many responders to the WTC disaster enabled us to generate a large gene expression data set of 355 donors, to our knowledge the largest single traumatic event expression data set to date. We used the Clinician-Administered PTSD Scale (CAPS) [14] score as a quantitative measure of PTSD symptom severity rather than a case/control definition, thus substantially increasing statistical power in this study [15–17]. To our knowledge, ours is the first gene expression study to incorporate total PTSD symptom severity and PTSD symptom dimensions as outcomes ascertained with the CAPS, administered by trained clinicians. Further, we employed the five-factor model of PTSD symptoms, which further differentiates the hyperarousal cluster into dysphoric arousal and anxious arousal dimensions [11, 18, 19].

Table 1. Demographic and other characteristics.

	Mean (SD) or *N* (%)	
Age (years)	54.1 (8.3)	*Mean (SD)*
Number of years post-9/11 sample collected	13 (2.3)	*Mean (SD)*
BMI	30.1 (5.9)	*Mean (SD)*
Male sex	291 (82)	*N (%)*
Current smoker	22 (6.2)	*N (%)*
High school graduate	301 (84.9)	*N (%)*
Annual income > $90,000	178 (50.1)	*N (%)*
Responder type		
Police responder	145 (40.8)	*N (%)*
Non-traditional responder	210 (59.2)	*N (%)*
Race-ethnicity		
African American	64 (18)	*N (%)*
Asian	5 (1.4)	*N (%)*
Hispanic	72 (20.3)	*N (%)*
Native American	9 (2.5)	*N (%)*
European American (White)	216 (60.8)	*N (%)*
Other	8 (2.3)	*N (%)*

$n = 355$.
SD standard deviation, *BMI* body mass index.

METHODS

Participants

The WTC Health Program (WTC-HP) is a regional consortium of five clinical centers established in the greater New York City area by the Centers of Disease Control and Prevention in 2002, with the goal of providing health monitoring and treatment to WTC responders, comprising the WTC-HP General Responder Cohort [20]. We recruited participants from the WTC-HP Responder Cohort who had completed at least three periodic health monitoring visits at one of the four WTC-HP clinical centers participating in this study – Mount Sinai Medical Center, New York University, Northwell Health, and Rutgers/The State University of New Jersey – and who had provided signed consent to be contacted for research studies. Stratified random sampling was employed to ensure selection of WTC responders spanning the full range of WTC-related PTSD symptom severity, from no/minimal symptoms to severe/chronic PTSD symptom levels on the PTSD Checklist – Specific Version (PCL-S) [21] completed during periodic health monitoring visits to the WTC-HP. Individuals with a lifetime history of chronic psychotic disorder or bipolar disorder type I, substance abuse/dependence or alcohol dependence over the prior three months, current pregnancy, acute medical illness or exacerbation of chronic medical illness, history of significant head injury or cerebrovascular accident, changes in central nervous system-active medications or medication dosages over the prior month, or who were taking oral or regularly injected steroid medications were excluded from the study.

The study, conducted between April 2013 and September 2017, was approved by the Institutional Review Board of the Icahn School of

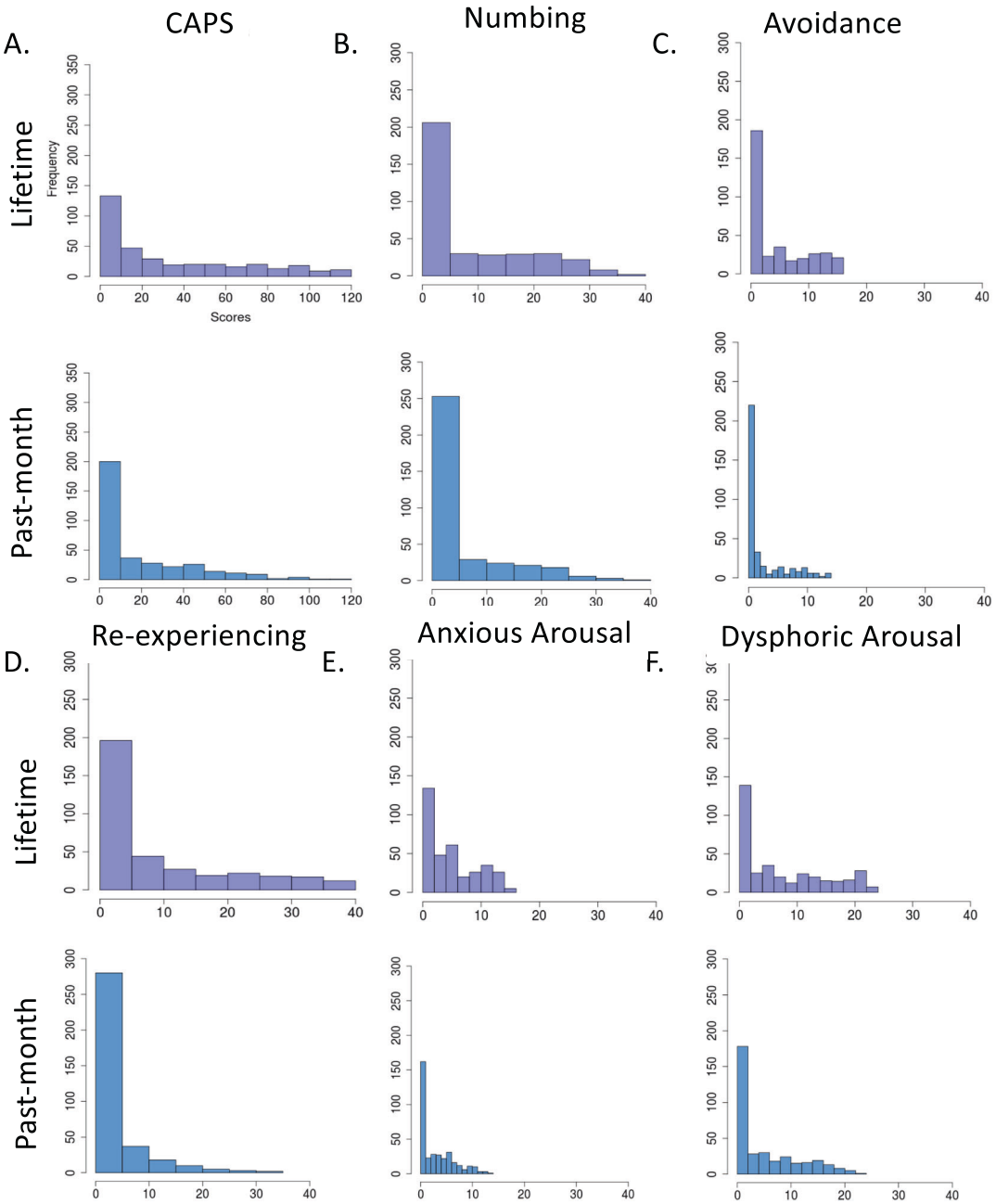

Fig. 1 Distribution of lifetime and past-month severity scores for Clinician-Administered PTSD Scale (CAPS) and PTSD-symptom dimensions. Distribution scores are separated into (**A**) CAPS, (**B**) numbing, (**C**) avoidance, (**D**) re-experiencing, (**E**) anxious arousal and (**F**) dysphoric arousal. PTSD symptom dimensions are scored from 0 to 50, and CAPS is an aggregate of that score. Total $N = 355$ World Trade Center responders.

Medicine at Mount Sinai, and all participants provided written informed consent. A total of 471 WTC responders completed in-person clinical assessments, yielding a final sample of 371 participants who met study eligibility criteria and completed study procedures, and 355 of those who had viable RNA-sequencing data. The mean age of participants was 54.1 (SD = 8.3) years, 82% were male; ethnicity proportions are given in Table 1. The sample was composed of 40.8% police responders and 59.2% non-traditional responders (e.g., construction workers).

Assessments

Data on 10 WTC-related exposures [22] (e.g., exposed to human remains, received treatment for an illness/injury during WTC recovery work) was obtained from interviews and self-report questionnaires completed by participants during their first health-monitoring visit to the WTC-HP, an average of 4.3 (SD = 2.7) years following 9/11/2001. In-person clinical assessments were conducted an average of 13.0 (SD = 1.3) years following 9/11/2011. Trained Masters- or PhD-level clinical interviewers administered the Structured Clinical Interview for DSM-IV (SCID) [1] to assess current and lifetime Axis-I psychiatric diagnoses, and CAPS [14], lifetime and past-month versions, to assess lifetime and past-month WTC-related PTSD diagnostic status and WTC-related PTSD symptom severity. Lifetime and past-month PTSD diagnosis was defined as meeting DSM-IV criteria for WTC-related PTSD and a total score ≥ 40 on the lifetime and past-month CAPS, respectively. CAPS DSM-IV was used rather than the current DSM-V definition due to consistency and timing of the study.

On the same day as the clinical assessment, participants also completed the Childhood Trauma Questionnaire (CTQ) [23], assessing physical, sexual,

and emotional abuse, and physical and emotional neglect experienced in childhood; the Traumatic Life Events Questionnaire (TLEQ) [24], assessing lifetime exposure to a range of traumatic events (e.g, crime, natural disaster, assault); a checklist of 15 stressful life events they might have experienced since 9/11/2011 (e.g., "lost a job/laid off/lost income", "divorced from spouse", "had debt trouble"), modified from the Diagnostic Interview Schedule (DIS) Disaster Supplement [25]; and a health questionnaire asking which medical conditions they had ever been diagnosed with [26], modified to add common WTC-related conditions (asthma or chronic respiratory condition, chronic rhinitis or sinusitis, sleep apnea, or acid reflux). Participants additionally completed a history and physical examination conducted by a licensed nurse practitioner, as well as routine laboratory testing, to rule out acute medical illness or exacerbation of chronic medical illness.

Among the 355 participants, 108 were determined to have met DSM-IV criteria for lifetime WTC-related PTSD, with 53 of them still meeting past-month PTSD criteria. The heterogeneity of PTSD confers some problems when attempting to analyze the disorder by case/control status alone. Case/control analyses do not fully capture the symptom complexity of the disorder, resulting in poor genomic modeling. Similarly, while overall PTSD symptom severity is a better quantitative measurement, it does not fully capture variability across PTSD symptomatology on a useful clinical level [18]. To address this variability, we examined five symptom dimensions (re-experiencing, avoidance, emotional numbing, dysphoric arousal and anxious arousal symptoms), assessed with the CAPS DSM-IV, to more accurately examine the heterogeneity of PTSD symptomatology (Fig. 1) [11].

Blood sample collection and RNA extraction

Participants were instructed to fast after midnight and underwent collection of blood samples between 8:00 and 10:00 am. Total RNA was purified from whole blood collected in PAXgene blood RNA tubes (Qiagen, Germantown, MD, USA) using a PAXgene blood RNA kit IVD (Qiagen, Germantown, MD, USA). Total RNA concentration and quality were estimated using a NanoDrop 200c spectrophotometer according to the manufacturer instructions (Thermo Fisher Scientific, Waltham, MA, USA). Samples with an optical density ratio 260/280 superior or equal to 1.8 passed the quality control. Total RNA concentration and quality were also estimated using an Agilent RNA 6000 nano kit and an Agilent 2100 bioanalyzer according to the manufacturer instructions (Agilent Technologies, Santa Clara, CA, USA). Samples with an RNA Integrity Number superior or equal to 7 passed the quality control. RNA samples (derived from blood) were processed for RNA Seq with polyA selection and sequenced on Illumina HiSeq High Output mode with a sequencing configuration of 2×150 paired-end reads (GENEWIZ, South Plainfield, NJ). A total of 10 M paired reads per sample was set as a threshold to account for high globin reads; 29 samples were re-sequenced to meet threshold.

Gene expression quality control analysis

We processed whole-blood gene expression data using the RAPiD.19 RNA-sequencing pipeline, and calculated normalized TPM counts from RSEM [27]. We performed quality control analysis on the counts to verify sequencing and residual contributions to variance using VariancePartition [28]. We corrected each sequencing batch for sex, age, and genotype-derived principal components using Limma/voom weighted least-squares linear regression [29]. We rank normalized and combined the residuals from the linear regression of each batch, and these values were used in all subsequent association tests for CAPS DSM-IV total score and five PTSD dimension scores (re-experiencing, avoidance, numbing, dysphoric arousal and anxious arousal).

Differential gene expression analysis

We used whole blood RNA-sequencing to test for associations between gene expression and WTC-related PTSD symptom severity on (i) highest lifetime CAPS DSM-IV score (lifetime CAPS), (ii) past-month CAPS score (past-month CAPS), and (iii) PTSD dimension scores including re-experiencing, avoidance, numbing, dysphoric arousal and anxious arousal, correcting for batch and surrogate variables using Surrogate Variable Analysis [30] (Eq. (1)).

$$\text{Gene expression} \sim \text{Dx} + \text{batch} + \text{surrogate variables} \quad (1)$$

Equation (1). General equation for gene expression analysis.

In addition, study participants had a wide range of psychiatric and somatic comorbidities, including some with substantial shared genetic aetiology and overlapping symptom profiles; comorbidities that may represent systemic manifestations of PTSD (e.g., cardiovascular disease [31]); and exposure to the dust cloud during and following 9/11. We expect all of these factors to have substantial impacts on gene expression. Significant co-linearity between some of these measures and CAPS scores preclude including these variables as covariates within our analysis, and testing directly for their effect on gene expression (in particular, due to significant correlations between length of time at the WTC site, PTSD symptom severity, and dust-cloud exposure [19, 32, 33]; and between PTSD symptom severity and co-morbid medical disorders potentially constituting systemic manifestations of PTSD [34–36]). Instead, in order to test whether these comorbidities and exposures might account for some of the CAPS-expression associations we observe, we also tested for gene expression associations with (i) an index of dust cloud exposure [37]; and (ii) number of medical comorbidities. Next, we tested for (i) interaction effects between each of these measures and CAPS score; (ii) enrichment of genome-wide significant associations between these measures and CAPS score; and (iii) genome-wide correlations in association statistics. For all gene expression analyses, we established significance using a Benjamini–Hochberg [38] FDR correction <5%.

Gene-set enrichment of PTSD-associated genes

We tested for gene set enrichment among our genes associated with lifetime CAPS DSM-IV, past-month CAPS, and PTSD symptom dimension scores by (i) analyzing the significant genes from the association tests for pathway enrichment by gene permutation testing and (ii) analyzing all genes from the ranked association test gene lists to subject permutation using the R versions of GSEA [39] and fgsea [40, 41]. For gene permutation testing, we included all FDR significant genes ($p < 0.05$), and tested for association with 105 gene sets using Kyoto Encyclopedia of Genes and Genomes (KEGG) database [42] for pathway enrichment.

We applied phenotype permutation testing rather than gene set permutation to keep the correlations between the genes in the dataset and the genes in the gene set pathways. For the subject permutation

Table 2. Gene expression studies included in meta-analysis.

Trauma study	ISMMS	WTC-d [3]	WTC-r [3]	TMA-C [10]	TMA-MI [10]	TMA-FI [10]
Past-month PTSD/control, *N* subjects	53/302	57/138	24/63	N/A	N/A	N/A
Lifetime PTSD/Control, *N* subjects	108/247	N/A	N/A	85/84	45/67	99/160
Total N subjects	355	195	87	169	112	259
Available genes ($p < 0.05$), *N*	1016	27	27	806	418	418
Age, Mean	54.1 (8.3)	52 (8.12)	52 (8.12)	24.4 (4.7)	41.1 (12.8)	39.5 (12.3)
Male, *N* (%)	291 (82)	195 (100)	87 (100)	169 (100)	112 (100)	0 (0)
European American, *N* (%)	216 (60.8)	165 (84.6)	74 (84.6)	108 (63.6)	34 (30.3)	62 (23.9)
African American, *N* (%)	64 (18)	N/A	N/A	N/A	78 (69.7)	197 (76.1)
Hispanic, *N* (%)	72 (20.3)	N/A	N/A	N/A	N/A	N/A

ISMMS Icahn School of Medicine at Mount Sinai (this study), *WTC-d* Stony Brook World Trade Center discovery cohort, *WTC-r* Stony Brook World Trade Center replication cohort, *TMA-C* Trauma mega-analysis combat cohort, *TMA-MI* Trauma mega-analysis male-interpersonal cohort, *TMA-FI* Trauma mega-analysis female-interpersonal cohort.

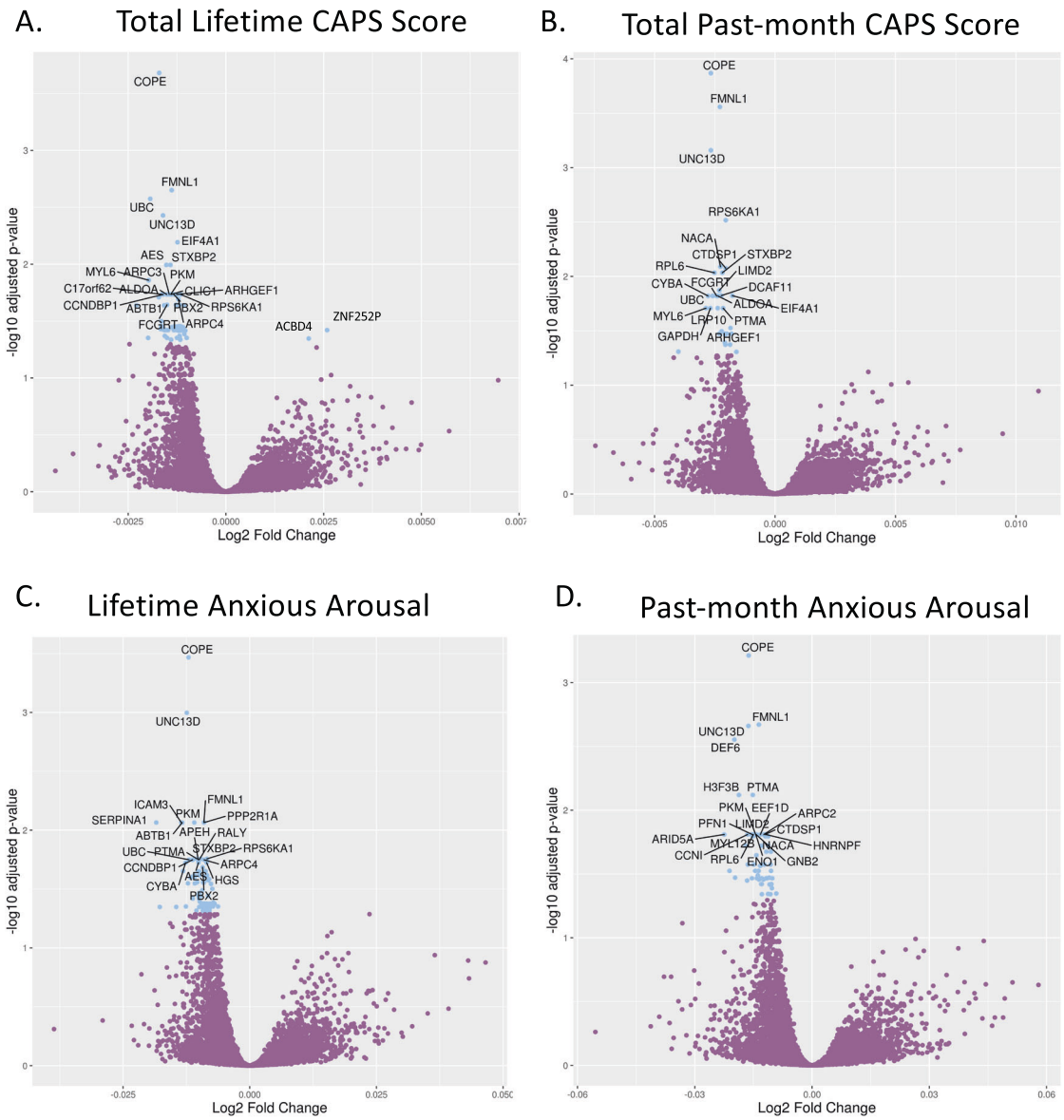

Fig. 2 Differential gene expression analysis of lifetime Clinician-Administered PTSD Scale (CAPS), CAPS past-month, anxious arousal lifetime and anxious arousal past-month in $N = 355$ World Trade Center first-responders. Total number of differentially expressed genes ($p < 0.05$): (**A**) Lifetime CAPS $N = 66$, (**B**) CAPS past-month $N = 31$, (**C**) anxious arousal lifetime $N = 86$, (**D**) anxious arousal past-month $N = 61$. Phenotypes were corrected for sex, age, batch, and first 10 ancestry principal components.

testing, each test was run with 10000 permutations, and pathways that passed Benjamini–Hochberg multiple testing correction were considered significantly enriched. To synthesize this large amount of gene set information, we generated comparative PTSD symptom plots using Clusterprofiler [43] in R. Comparative gene set plots contained pathways which passed FDR < 0.05 significance threshold.

Meta-analysis with existing gene expression analyses

To replicate our gene expression results, we meta-analyzed our data with association statistics from five other genome-wide gene expression analyses:

1. WTC responder study Stony Brook University (SB WTC) [3]; $N = 282$. Data are divided into discovery (WTC-d) and replication (WTC-r) cohorts.
2. Trauma Mega-Analysis study (TMA) [10]. TMA combines 5 different PTSD studies: childhood [44], assault [45], emergency room [46], interpersonal [44], and combat studies [45, 47, 48]. In the original mega-analysis, these 5 studies were combined and transformed into three distinct categories: combat ($N = 169$), male interpersonal ($N = 112$), and female interpersonal trauma ($N = 259$) [10]. We analyzed these data as separate trauma studies for the purposes of our meta-analysis (Table 2).

Since the majority of studies focus on PTSD case/control status, rather than associations with continuous CAPS scores (as here), we repeated our analysis to compare gene expression between PTSD cases (defined as meeting DSM-IV criteria for PTSD and a total CAPS ≥ 40) and controls (all others in our sample).

We meta-analyzed PTSD case-control association statistics using a sample-size-based meta-analysis approach in METAL [49]. We included all genes from our analysis that reached $p < 0.05$ ($N = 9380$ for past-month and $N = 1016$ for lifetime) and all available genes from other studies ($N =$ 27–806; Table 2).

Cellular deconvolution associated with CAPS scores

We applied CIBERSORT to our raw counts matrix to deconvolute immune cell types in our patients using the immune cell-matrix reference panel LM22 [50]. We tested for association between cell-type proportions and past-month CAPS, lifetime CAPS.

Table 3. Bivariate correlations between lifetime and past-month Clinician-Administered PTSD Scale (CAPS) scores and PTSD symptom dimensions.

Lifetime vs. Past-month	R^2 (of beta values)	p	R^2 (of FDR-adjusted P values)	p	
Total CAPS score	0.82	$<2.2\times10^{-16}$	0.79	$<2.2\times10^{-16}$	
Re-experiencing	0.66	$<2.2\times10^{-16}$	0.63	$<2.2\times10^{-16}$	
Anxious Arousal	0.8	$<2.2\times10^{-16}$	0.77	$<2.2\times10^{-16}$	
Avoidance	0.73	$<2.2\times10^{-16}$	0.71	$<2.2\times10^{-16}$	
Dysphoric Arousal	0.75	$<2.2\times10^{-16}$	0.72	$<2.2\times10^{-16}$	
Numbing	0.66	$<2.2\times10^{-16}$	0.64	$<2.2\times10^{-16}$	
Bivariate correlations between PTSD symptom dimensions					
Past-month	Re-experiencing	Anxious arousal	Avoidance	Dysphoric arousal	Numbing
Re-experiencing	1	0.53	0.63	0.59	0.62
	Anxious arousal	1	0.57	0.64	0.55
		Avoidance	1	0.61	0.63
			Dysphoric arousal	1	0.71
				Numbing	1
Lifetime	Re-experiencing	Anxious arousal	Avoidance	Dysphoric arousal	Numbing
Re-experiencing	1	0.72	0.79	0.75	0.73
	Anxious arousal	1	0.71	0.73	0.69
		Avoidance	1	0.74	0.79
			Dysphoric arousal	1	0.78
				Numbing	1

CAPS Clinician-Administered PTSD Scale, *FDR* false discovery rate.

Table 4. Comorbid medical conditions.

Conditions	N (%)
Hypertension	162 (45.6)
Cardiac disease	28 (7.9)
Diabetes	44 (12.4)
GERD	184 (51.8)
Chronic pain	144 (40.6)
Arthritis	138 (38.9)
Asthma	161 (45.4)
Cancer	51 (14.4)
Chronic rhinitis	169 (47.6)
Sleep apnea	127 (35.8)
Kidney disease	8 (2.3)
Chronic skin condition	70 (19.7)
High cholesterol	174 (49)
Liver disease	15 (4.3)
Migraine	50 (14.1)
Osteoporosis	11 (3.1)
Rheumatoid Arthritis	15 (4.3)
Stroke	4 (1.1)
Traumatic brain injury	5 (1.4)

GERD gastroesophageal reflux disease.

RESULTS

Gene expression is associated with PTSD symptom levels in WTC first responders

We tested for association between expression of 12,220 genes and total CAPS DSM-IV score in a sample of 355 WTC responders. We identified 31 genes significantly associated with total past-month CAPS score (Fig. 2), and 66 genes associated with lifetime (highest) CAPS score (Fig. 2). Significance was determined using a Benjamini–Hochberg [38] FDR correction <5%. Of these, 42/66 genes were associated only with lifetime CAPS, (and not past-month CAPS), while 7/31 genes were associated only with past-month CAPS, (and not lifetime CAPS). Genome-wide associations with past-month CAPS and lifetime CAPS were significantly correlated (Beta $\rho = 0.82$, $p < 2.2\times10^{-16}$; FDR-adjusted P values $\rho = 0.79$, $p < 2.2\times10^{-16}$) (Table 3).

We tested for enrichment of 59 well-studied PTSD candidate genes including genes from the most recent PGC-PTSD GWAS [9, 51] and gene expression analysis [52] (Supplementary Table 1) within our association statistics. We did not observe enrichment of these genes within our past-month or lifetime association analyses ($p = 0.174$, 0.245). However, of these candidate genes, *SERPINA1* was significantly associated with lifetime CAPS score.

Environmental exposure to the WTC dust cloud

Next, we tested whether our genes associated with CAPS DSM-IV scores are specific to PTSD, or are driven by spurious associations with comorbid diagnoses or environmental exposure to the dust cloud at Ground Zero. In particular, a number of individuals within our study have comorbid conditions and complex medical histories (Table 4), including disorders with substantial shared genetic and environmental etiology with PTSD, and disorders and traits that may present as systemic manifestations of PTSD.

First, we tested whether these medical comorbidities alone may account for the associations we observe; we identified 175 gene associations with an aggregate summary score of medical comorbidities. Again, significance was determined using a Benjamini–Hochberg [38] FDR correction <5%. Notably, these genes do not include any of our significant associations with CAPS scores. We identified only one gene, *STX10*, with significant interaction between CAPS scores and comorbid medical conditions; that is, gene expression was elevated specifically among individuals with both high lifetime CAPS and a large number of comorbid medical diagnoses (Fig. 3).

Next, we tested for association between gene expression and exposure to the dust cloud at Ground Zero [37]. We identified 561

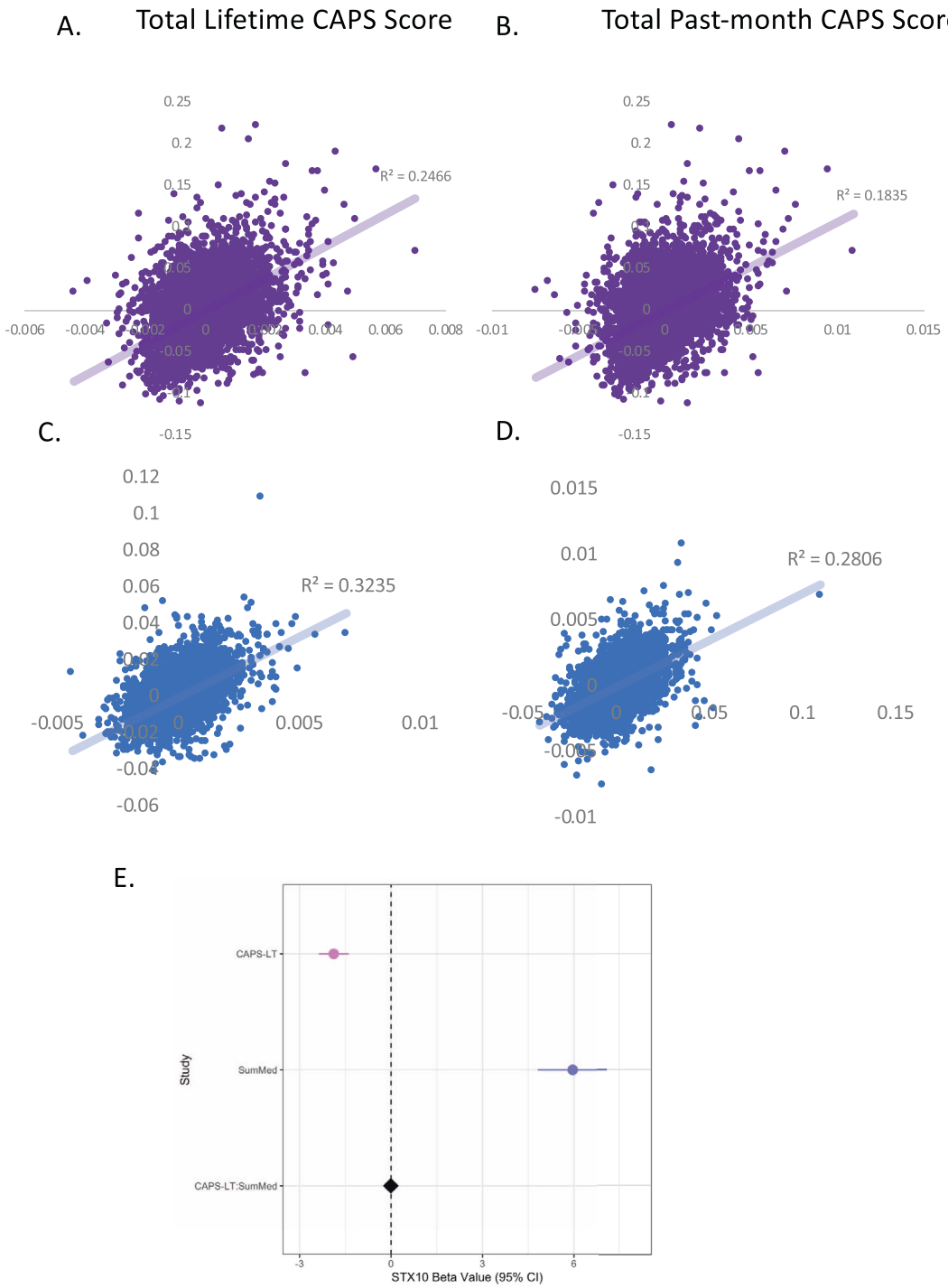

Fig. 3 Dust cloud severity and disease comorbidity of Clinician-Administered PTSD Scale (CAPS) lifetime and past-month genome-wide correlations. A Lifetime CAPS score correlation to dust cloud severity, (**B**) Past-month CAPS score correlation to dust cloud severity, (**C**) Lifetime CAPS score correlation to disease comorbidity, (**D**) Past-month CAPS score correlation to disease comorbidity, (**E**) Interaction term, *STX10*, of disease comorbidity and CAPS lifetime. *SumMed* summary of medical terms for disease comorbidity, *CAPS-LT* CAPS lifetime.

genes significantly associated with this exposure. We tested for, but did not find, any significant interactions between CAPS scores and dust cloud exposure ($p > 0.05$), and did not observe a large correlation of expression results in genome-wide significant genes between the two analyses for past-month CAPS or lifetime CAPS ($R^2 = 0.1835$, $R^2 = 0.2466$, $p < 0.05$) (Fig. 3). Together, these analyses imply that our gene-CAPS score associations are specific and relevant to PTSD, rather than due to confounding by comorbid diagnoses or dust cloud exposure.

Gene expression analysis reveals PTSD dimension-specific associations

Next, we tested for gene expression associations with past-month and lifetime PTSD symptom dimensions (re-experiencing, avoidance, dysphoric arousal, anxious arousal, numbing; Table 5). Our analysis revealed overlapping and unique genes for each symptom dimension, and significant correlation of genome-wide association statistics between symptom dimensions. In particular, both our past-month and lifetime analyses identified a large

Table 5. Gene expression associations with Clinician-Administered PTSD Scale (CAPS) score and PTSD symptom dimensions.

a. Lifetime CAPS score

Log2 fold-change	Average expression	t-statistic	P value	Adjusted P value	Beta coefficient	Gene symbol	Phenotype
−0.0017	−0.149	−5.776	1.79E-08	0.0002	6.11	COPE	CAPS
−0.0014	−0.177	−5.192	3.68E-07	0.0022	3.16	FMNL1	CAPS
−0.0019	−0.174	−5.072	6.63E-07	0.0027	2.59	UBC	CAPS
−0.0016	−0.157	−4.939	1.26E-06	0.0038	1.98	UNC13D	CAPS
−0.0012	−0.157	−4.777	2.70E-06	0.0066	1.24	EIF4A1	CAPS
−0.0014	−0.169	−4.609	5.83E-06	0.0101	0.50	STXBP2	CAPS
−0.0015	−0.147	−4.611	5.77E-06	0.0101	0.50	AES	CAPS
−0.0020	−0.204	−4.503	9.34E-06	0.0142	0.04	MYL6	CAPS
−0.0014	−0.164	−4.287	2.39E-05	0.0187	−0.86	PKM	CAPS
−0.0013	−0.170	−4.325	2.03E-05	0.0187	−0.70	ARHGEF1	CAPS
−0.0014	−0.194	−4.267	2.60E-05	0.0187	−0.94	ARPC3	CAPS
−0.0012	−0.169	−4.301	2.25E-05	0.0187	−0.80	RPS6KA1	CAPS
−0.0015	−0.190	−4.268	2.59E-05	0.0187	−0.93	ALDOA	CAPS
−0.0016	−0.152	−4.403	1.45E-05	0.0187	−0.38	CCNDBP1	CAPS
−0.0016	−0.166	−4.317	2.10E-05	0.0187	−0.74	C17orf62	CAPS
−0.0013	−0.143	−4.345	1.87E-05	0.0187	−0.62	PBX2	CAPS
−0.0014	−0.185	−4.338	1.92E-05	0.0187	−0.65	CLIC1	CAPS
−0.0017	−0.184	−4.243	2.87E-05	0.0195	−1.03	ABTB1	CAPS
−0.0012	−0.182	−4.219	3.18E-05	0.0204	−1.13	ARPC4	CAPS
−0.0013	−0.154	−4.179	3.76E-05	0.0229	−1.29	RXRA	CAPS
−0.0015	−0.172	−4.156	4.14E-05	0.0229	−1.38	FCGRT	CAPS
−0.0012	−0.160	−4.160	4.07E-05	0.0229	−1.37	ARAP1	CAPS
−0.0016	−0.193	−4.131	4.61E-05	0.0232	−1.48	TYROBP	CAPS
−0.0011	−0.156	−4.122	4.76E-05	0.0232	−1.51	RTFDC1	CAPS
−0.0023	−0.164	−4.123	4.75E-05	0.0232	−1.51	SERPINA1	CAPS
−0.0016	−0.138	−4.031	6.91E-05	0.0324	−1.87	FURIN	CAPS
−0.0016	−0.194	−4.003	7.75E-05	0.0350	−1.98	GAPDH	CAPS
−0.0017	−0.194	−3.962	9.15E-05	0.0355	−2.14	CYBA	CAPS
−0.0012	−0.173	−3.978	8.57E-05	0.0355	−2.07	GNAI2	CAPS
−0.0013	−0.166	−3.973	8.75E-05	0.0355	−2.09	OS9	CAPS
−0.0012	−0.171	−3.984	8.36E-05	0.0355	−2.05	CD53	CAPS
−0.0012	−0.165	−3.957	9.33E-05	0.0355	−2.15	GRK6	CAPS
−0.0014	−0.180	−3.945	9.78E-05	0.0361	−2.20	ARHGDIB	CAPS
−0.0011	−0.175	−3.936	1.01E-04	0.0363	−2.23	RHOA	CAPS
−0.0013	−0.170	−3.909	1.13E-04	0.0372	−2.33	ENO1	CAPS
−0.0017	−0.195	−3.912	1.11E-04	0.0372	−2.32	YPEL3	CAPS
−0.0012	−0.164	−3.922	1.07E-04	0.0372	−2.29	DAZAP2	CAPS
−0.0013	−0.171	−3.900	1.17E-04	0.0375	−2.37	PTMA	CAPS
−0.0016	−0.199	−3.891	1.21E-04	0.0379	−2.40	ICAM3	CAPS
−0.0012	−0.116	−3.851	1.41E-04	0.0379	−2.55	SNX1	CAPS
−0.0013	−0.129	−3.829	1.55E-04	0.0379	−2.63	DCAF11	CAPS
−0.0012	−0.064	−3.847	1.44E-04	0.0379	−2.56	ASH2L	CAPS
−0.0016	−0.183	−3.854	1.40E-04	0.0379	−2.54	H3F3B	CAPS
−0.0015	−0.183	−3.827	1.56E-04	0.0379	−2.64	FLOT2	CAPS
−0.0015	−0.147	−3.869	1.32E-04	0.0379	−2.48	TAF10	CAPS
−0.0011	−0.138	−3.840	1.48E-04	0.0379	−2.59	STAT3	CAPS
−0.0013	−0.191	−3.856	1.39E-04	0.0379	−2.53	CFL1	CAPS
−0.0011	−0.119	−3.848	1.43E-04	0.0379	−2.56	EVL	CAPS
0.0026	0.086	3.834	1.51E-04	0.0379	−2.61	ZNF252P	CAPS
−0.0016	−0.148	−3.879	1.27E-04	0.0379	−2.45	GSTK1	CAPS
−0.0012	−0.110	−3.818	1.61E-04	0.0385	−2.67	RPS6KB2	CAPS

Table 5. continued

a. Lifetime CAPS score

Log2 fold-change	Average expression	t-statistic	P value	Adjusted P value	Beta coefficient	Gene symbol	Phenotype
−0.0012	−0.164	−3.811	1.65E-04	0.0388	−2.70	LRCH4	CAPS
−0.0010	−0.125	−3.803	1.71E-04	0.0392	−2.73	PPP2R1A	CAPS
−0.0011	−0.136	−3.783	1.84E-04	0.0416	−2.80	FAM49B	CAPS
−0.0012	−0.172	−3.762	2.00E-04	0.0435	−2.87	WBP2	CAPS
−0.0016	−0.162	−3.766	1.97E-04	0.0435	−2.86	EHBP1L1	CAPS
−0.0012	−0.174	−3.757	2.04E-04	0.0436	−2.89	TPM3	CAPS
−0.0012	−0.162	−3.733	2.23E-04	0.0450	−2.98	TPI1	CAPS
−0.0015	−0.167	−3.727	2.29E-04	0.0450	−3.00	PLCB2	CAPS
−0.0010	−0.167	−3.730	2.26E-04	0.0450	−2.99	ARF1	CAPS
−0.0013	−0.169	−3.730	2.26E-04	0.0450	−2.99	GNB2	CAPS
−0.0020	−0.123	−3.729	2.27E-04	0.0450	−3.00	ARID5A	CAPS
−0.0012	−0.158	−3.722	2.33E-04	0.0451	−3.02	CHMP2A	CAPS
−0.0014	−0.164	−3.705	2.48E-04	0.0458	−3.08	PARVG	CAPS
0.0021	0.041	3.707	2.46E-04	0.0458	−3.07	ACBD4	CAPS
−0.0012	−0.181	−3.710	2.44E-04	0.0458	−3.06	NACA	CAPS
−0.0051	−0.149	−5.227	3.09E-07	0.0038	4.51	COPE	Re-experiencing
−0.0060	−0.174	−4.819	2.22E-06	0.0135	2.60	UBC	Re-experiencing
−0.0057	−0.193	−4.616	5.63E-06	0.0229	1.71	TYROBP	Re-experiencing
−0.0038	−0.157	−4.537	8.03E-06	0.0245	1.36	EIF4A1	Re-experiencing
−0.0069	−0.149	−5.023	8.39E-07	0.0102	3.88	COPE	Dysphoric arousal
−0.0070	−0.157	−4.710	3.68E-06	0.0112	2.45	UNC13D	Dysphoric arousal
−0.0079	−0.152	−4.788	2.56E-06	0.0112	2.80	CCNDBP1	Dysphoric arousal
−0.0059	−0.177	−4.770	2.78E-06	0.0112	2.72	FMNL1	Dysphoric arousal
−0.0080	−0.174	−4.554	7.44E-06	0.0151	1.78	UBC	Dysphoric arousal
−0.0054	−0.157	−4.588	6.39E-06	0.0151	1.92	EIF4A1	Dysphoric arousal
−0.0090	−0.204	−4.499	9.52E-06	0.0166	1.54	MYL6	Dysphoric arousal
−0.0080	−0.184	−4.357	1.77E-05	0.0270	0.94	ABTB1	Dysphoric arousal
−0.0060	−0.154	−4.287	2.39E-05	0.0324	0.66	RXRA	Dysphoric arousal
−0.0064	−0.121	−4.236	2.97E-05	0.0362	0.45	NFYC	Dysphoric arousal
−0.0051	−0.169	−4.174	3.85E-05	0.0427	0.20	RPS6KA1	Dysphoric arousal
−0.0064	−0.194	−4.130	4.62E-05	0.0469	0.03	ARPC3	Dysphoric arousal
−0.0062	−0.129	−4.109	5.03E-05	0.0471	−0.05	DCAF11	Dysphoric arousal
0.0126	0.086	4.092	5.41E-05	0.0471	−0.12	ZNF252P	Dysphoric arousal
−0.0071	−0.150	−4.048	6.47E-05	0.0493	−0.29	TNFSF10	Dysphoric arousal
−0.0066	−0.190	−4.051	6.39E-05	0.0493	−0.28	ALDOA	Dysphoric arousal
−0.0121	−0.149	−5.693	2.80E-08	0.0003	7.62	COPE	Anxious arousal
−0.0124	−0.157	−5.351	1.65E-07	0.0010	5.89	UNC13D	Anxious arousal
−0.0109	−0.164	−4.655	4.73E-06	0.0086	2.65	PKM	Anxious arousal
−0.0135	−0.199	−4.720	3.50E-06	0.0086	2.94	ICAM3	Anxious arousal
−0.0090	−0.125	−4.645	4.95E-06	0.0086	2.61	PPP2R1A	Anxious arousal
−0.0090	−0.177	−4.685	4.12E-06	0.0086	2.78	FMNL1	Anxious arousal
−0.0185	−0.164	−4.672	4.37E-06	0.0086	2.73	SERPINA1	Anxious arousal
−0.0133	−0.184	−4.615	5.66E-06	0.0086	2.48	ABTB1	Anxious arousal
−0.0097	−0.169	−4.383	1.58E-05	0.0175	1.49	STXBP2	Anxious arousal
−0.0085	−0.169	−4.384	1.57E-05	0.0175	1.50	RPS6KA1	Anxious arousal
−0.0104	−0.171	−4.400	1.47E-05	0.0175	1.57	PTMA	Anxious arousal
−0.0100	−0.161	−4.292	2.34E-05	0.0178	1.12	RALY	Anxious arousal
−0.0120	−0.174	−4.328	2.00E-05	0.0178	1.27	UBC	Anxious arousal
−0.0102	−0.091	−4.292	2.34E-05	0.0178	1.12	APEH	Anxious arousal
−0.0113	−0.152	−4.310	2.16E-05	0.0178	1.19	CCNDBP1	Anxious arousal
−0.0090	−0.182	−4.356	1.78E-05	0.0178	1.38	ARPC4	Anxious arousal

Table 5. continued

a. Lifetime CAPS score

Log2 fold-change	Average expression	t-statistic	P value	Adjusted P value	Beta coefficient	Gene symbol	Phenotype
−0.0127	−0.194	−4.238	2.94E-05	0.0189	0.90	CYBA	Anxious arousal
−0.0101	−0.147	−4.248	2.81E-05	0.0189	0.94	AES	Anxious arousal
−0.0085	−0.126	−4.243	2.88E-05	0.0189	0.92	HGS	Anxious arousal
−0.0093	−0.143	−4.204	3.39E-05	0.0207	0.77	PBX2	Anxious arousal
−0.0087	−0.170	−4.163	4.02E-05	0.0223	0.60	ARHGEF1	Anxious arousal
−0.0132	−0.204	−4.167	3.95E-05	0.0223	0.62	MYL6	Anxious arousal
−0.0100	−0.183	−4.141	4.41E-05	0.0224	0.52	LIMD2	Anxious arousal
−0.0102	−0.191	−4.148	4.28E-05	0.0224	0.54	CFL1	Anxious arousal
−0.0100	−0.170	−4.104	5.14E-05	0.0242	0.37	ENO1	Anxious arousal
−0.0109	−0.168	−4.094	5.36E-05	0.0242	0.33	MYL12B	Anxious arousal
−0.0084	−0.160	−4.101	5.19E-05	0.0242	0.36	ARAP1	Anxious arousal
−0.0112	−0.193	−4.075	5.80E-05	0.0246	0.26	TYROBP	Anxious arousal
−0.0089	−0.164	−4.072	5.86E-05	0.0246	0.25	LRCH4	Anxious arousal
−0.0109	−0.179	−4.059	6.18E-05	0.0251	0.20	CNPY3	Anxious arousal
−0.0117	−0.179	−4.049	6.43E-05	0.0253	0.16	NCF4	Anxious arousal
−0.0080	−0.138	−4.034	6.85E-05	0.0261	0.10	STAT3	Anxious arousal
−0.0082	−0.114	−4.021	7.22E-05	0.0267	0.05	HNRNPF	Anxious arousal
−0.0092	−0.122	−3.990	8.15E-05	0.0277	−0.07	CALCOCO1	Anxious arousal
−0.0104	−0.172	−3.991	8.13E-05	0.0277	−0.07	FCGRT	Anxious arousal
−0.0090	−0.164	−3.989	8.19E-05	0.0277	−0.07	PIK3CD	Anxious arousal
−0.0122	−0.176	−3.971	8.82E-05	0.0283	−0.14	TMSB10	Anxious arousal
−0.0108	−0.166	−3.974	8.71E-05	0.0283	−0.13	C17orf62	Anxious arousal
−0.0076	−0.161	−3.962	9.15E-05	0.0286	−0.18	RAB7A	Anxious arousal
−0.0074	−0.157	−3.931	1.03E-04	0.0315	−0.29	EIF4A1	Anxious arousal
−0.0094	−0.166	−3.918	1.09E-04	0.0324	−0.34	OS9	Anxious arousal
−0.0100	−0.190	−3.899	1.17E-04	0.0341	−0.41	ALDOA	Anxious arousal
−0.0097	−0.095	−3.869	1.32E-04	0.0361	−0.52	XAB2	Anxious arousal
−0.0082	−0.140	−3.872	1.31E-04	0.0361	−0.51	ADD1	Anxious arousal
−0.0101	−0.170	−3.867	1.33E-04	0.0361	−0.53	LRP10	Anxious arousal
−0.0112	−0.183	−3.842	1.47E-04	0.0381	−0.62	H3F3B	Anxious arousal
−0.0100	−0.087	−3.842	1.47E-04	0.0381	−0.62	FDPS	Anxious arousal
−0.0098	−0.170	−3.820	1.60E-04	0.0406	−0.71	PFN1	Anxious arousal
−0.0072	−0.123	−3.811	1.66E-04	0.0413	−0.74	ARFGAP2	Anxious arousal
−0.0093	−0.117	−3.762	2.00E-04	0.0421	−0.92	PTPRC	Anxious arousal
−0.0085	−0.179	−3.772	1.92E-04	0.0421	−0.88	EEF1D	Anxious arousal
−0.0079	−0.173	−3.799	1.73E-04	0.0421	−0.78	GNAI2	Anxious arousal
−0.0078	−0.152	−3.757	2.04E-04	0.0421	−0.93	HNRNPA2B1	Anxious arousal
−0.0089	−0.158	−3.781	1.86E-04	0.0421	−0.85	CHMP2A	Anxious arousal
−0.0090	−0.177	−3.758	2.03E-04	0.0421	−0.93	RHOG	Anxious arousal
−0.0069	−0.142	−3.768	1.95E-04	0.0421	−0.89	XRCC6	Anxious arousal
−0.0072	−0.170	−3.761	2.00E-04	0.0421	−0.92	CDC42SE1	Anxious arousal
−0.0089	−0.011	−3.762	2.00E-04	0.0421	−0.92	IPO9	Anxious arousal
−0.0089	−0.109	−3.759	2.02E-04	0.0421	−0.93	DCTN1	Anxious arousal
−0.0073	−0.124	−3.717	2.37E-04	0.0445	−1.08	NCL	Anxious arousal
−0.0097	−0.156	−3.733	2.23E-04	0.0445	−1.02	DBNL	Anxious arousal
−0.0091	−0.150	−3.726	2.29E-04	0.0445	−1.04	PPP4C	Anxious arousal
−0.0073	−0.146	−3.725	2.30E-04	0.0445	−1.05	PSMB4	Anxious arousal
−0.0063	−0.144	−3.738	2.19E-04	0.0445	−1.00	FLII	Anxious arousal
−0.0126	−0.190	−3.719	2.35E-04	0.0445	−1.07	RPL12	Anxious arousal
−0.0083	−0.141	−3.704	2.49E-04	0.0449	−1.12	MYO9B	Anxious arousal

Table 5. continued

a. Lifetime CAPS score

Log2 fold-change	Average expression	t-statistic	P value	Adjusted P value	Beta coefficient	Gene symbol	Phenotype
−0.0145	−0.172	−3.701	2.52E-04	0.0449	−1.13	RPL8	Anxious arousal
−0.0093	−0.168	−3.695	2.58E-04	0.0449	−1.16	STAT6	Anxious arousal
−0.0081	−0.153	−3.710	2.44E-04	0.0449	−1.10	IL16	Anxious arousal
−0.0100	−0.176	−3.691	2.62E-04	0.0449	−1.17	HCLS1	Anxious arousal
−0.0178	−0.175	−3.688	2.65E-04	0.0449	−1.18	IFITM1	Anxious arousal
−0.0082	−0.154	−3.696	2.57E-04	0.0449	−1.15	RXRA	Anxious arousal
−0.0087	−0.179	−3.676	2.77E-04	0.0463	−1.22	NADK	Anxious arousal
−0.0080	−0.169	−3.670	2.83E-04	0.0466	−1.24	HNRNPC	Anxious arousal
−0.0105	−0.143	−3.653	3.03E-04	0.0482	−1.31	APLP2	Anxious arousal
−0.0079	−0.144	−3.644	3.12E-04	0.0482	−1.34	SUN2	Anxious arousal
−0.0093	−0.188	−3.647	3.09E-04	0.0482	−1.32	RPL19	Anxious arousal
−0.0081	−0.171	−3.658	2.97E-04	0.0482	−1.29	CD53	Anxious arousal
−0.0085	−0.185	−3.650	3.05E-04	0.0482	−1.31	CLIC1	Anxious arousal
−0.0080	−0.134	−3.629	3.31E-04	0.0492	−1.39	SF3B2	Anxious arousal
−0.0089	−0.194	−3.634	3.24E-04	0.0492	−1.37	ARPC3	Anxious arousal
−0.0083	−0.172	−3.631	3.28E-04	0.0492	−1.38	WBP2	Anxious arousal
−0.0054	−0.177	−5.814	1.45E-08	0.0002	7.55	FMNL1	Numbing
−0.0055	−0.157	−4.872	1.72E-06	0.0070	2.92	UNC13D	Numbing
−0.0051	−0.149	−4.875	1.71E-06	0.0070	2.93	COPE	Numbing
−0.0063	−0.174	−4.697	3.90E-06	0.0119	2.13	UBC	Numbing
−0.0042	−0.169	−4.489	9.95E-06	0.0243	1.23	RPS6KA1	Numbing
−0.0047	−0.169	−4.341	1.89E-05	0.0342	0.61	STXBP2	Numbing
−0.0048	−0.147	−4.140	4.43E-05	0.0342	−0.20	AES	Numbing
−0.0059	−0.194	−4.138	4.46E-05	0.0342	−0.20	GAPDH	Numbing
−0.0050	−0.166	−4.319	2.09E-05	0.0342	0.52	OS9	Numbing
−0.0060	−0.138	−4.187	3.64E-05	0.0342	−0.01	FURIN	Numbing
−0.0042	−0.158	−4.245	2.86E-05	0.0342	0.22	CTDSP1	Numbing
−0.0056	−0.166	−4.251	2.79E-05	0.0342	0.24	C17orf62	Numbing
−0.0043	−0.160	−4.271	2.56E-05	0.0342	0.33	ARAP1	Numbing
−0.0048	−0.171	−4.122	4.77E-05	0.0342	−0.27	PTMA	Numbing
−0.0044	−0.143	−4.123	4.75E-05	0.0342	−0.26	PBX2	Numbing
−0.0047	−0.185	−4.172	3.87E-05	0.0342	−0.07	CLIC1	Numbing
−0.0042	−0.182	−4.128	4.65E-05	0.0342	−0.24	ARPC4	Numbing
−0.0063	−0.204	−4.084	5.59E-05	0.0378	−0.42	MYL6	Numbing
−0.0057	−0.184	−4.058	6.21E-05	0.0380	−0.52	ABTB1	Numbing
−0.0061	−0.170	−4.057	6.23E-05	0.0380	−0.52	CCDC88B	Numbing
−0.0041	−0.170	−4.031	6.92E-05	0.0402	−0.62	ARHGEF1	Numbing
−0.0041	−0.174	−4.004	7.74E-05	0.0429	−0.73	ARHGAP30	Numbing
−0.0042	−0.116	−3.979	8.53E-05	0.0433	−0.82	SNX1	Numbing
−0.0036	−0.157	−3.982	8.44E-05	0.0433	−0.81	EIF4A1	Numbing
−0.0049	−0.180	−3.944	9.81E-05	0.0460	−0.95	ARHGDIB	Numbing
−0.0056	−0.167	−3.944	9.80E-05	0.0460	−0.95	PLCB2	Numbing
−0.0038	−0.175	−3.888	1.23E-04	0.0476	−1.16	RHOA	Numbing
−0.0038	−0.162	−3.905	1.14E-04	0.0476	−1.10	PXN	Numbing
−0.0039	−0.141	−3.883	1.25E-04	0.0476	−1.18	GMIP	Numbing
−0.0049	−0.172	−3.899	1.17E-04	0.0476	−1.12	FCGRT	Numbing
−0.0040	−0.173	−3.922	1.07E-04	0.0476	−1.04	GNAI2	Numbing
−0.0114	−0.178	−3.914	1.10E-04	0.0476	−1.07	LY6E	Numbing
−0.0104	−0.149	−5.402	1.27E-07	0.0016	6.05	COPE	Avoidance
−0.0096	−0.169	−4.438	1.25E-05	0.0380	1.63	GNB2	Avoidance

Table 5. continued

a. Lifetime CAPS score

Log2 fold-change	Average expression	t-statistic	P value	Adjusted P value	Beta coefficient	Gene symbol	Phenotype
−0.0109	−0.166	−4.442	1.22E-05	0.0380	1.65	C17orf62	Avoidance
−0.0080	−0.177	−4.539	7.97E-06	0.0380	2.06	FMNL1	Avoidance
−0.0085	−0.116	−4.305	2.21E-05	0.0443	1.08	SNX1	Avoidance
−0.0113	−0.138	−4.272	2.54E-05	0.0443	0.95	FURIN	Avoidance
−0.00731	−0.157	−4.306	2.21E-05	0.0443	1.08	EIF4A1	Avoidance

b. Past-month CAPS score

Log2 fold-change	Average expression	t-statistic	P value	Adjusted P value	Beta coefficient	Gene symbol	Phenotype
−0.003	−0.149	−5.862	1.12E-08	0.0001	6.993	COPE	CAPS
−0.002	−0.177	−5.600	4.56E-08	0.0003	5.625	FMNL1	CAPS
−0.003	−0.157	−5.345	1.70E-07	0.0007	4.343	UNC13D	CAPS
−0.002	−0.169	−4.987	1.00E-06	0.0030	2.627	RPS6KA1	CAPS
−0.002	−0.181	−4.730	3.35E-06	0.0082	1.461	NACA	CAPS
−0.002	−0.158	−4.683	4.15E-06	0.0084	1.254	CTDSP1	CAPS
−0.002	−0.169	−4.622	5.49E-06	0.0093	0.986	STXBP2	CAPS
−0.003	−0.180	−4.599	6.08E-06	0.0093	0.887	RPL6	CAPS
−0.002	−0.183	−4.489	9.94E-06	0.0135	0.415	LIMD2	CAPS
−0.002	−0.129	−4.419	1.35E-05	0.0150	0.119	DCAF11	CAPS
−0.002	−0.157	−4.421	1.34E-05	0.0150	0.126	EIF4A1	CAPS
−0.003	−0.194	−4.345	1.86E-05	0.0151	−0.187	CYBA	CAPS
−0.002	−0.172	−4.355	1.78E-05	0.0151	−0.145	FCGRT	CAPS
−0.002	−0.190	−4.351	1.81E-05	0.0151	−0.161	ALDOA	CAPS
−0.003	−0.174	−4.363	1.72E-05	0.0151	−0.113	UBC	CAPS
−0.003	−0.204	−4.236	2.97E-05	0.0197	−0.633	MYL6	CAPS
−0.003	−0.194	−4.245	2.85E-05	0.0197	−0.595	GAPDH	CAPS
−0.002	−0.171	−4.228	3.07E-05	0.0197	−0.664	PTMA	CAPS
−0.002	−0.170	−4.255	2.74E-05	0.0197	−0.556	LRP10	CAPS
−0.002	−0.170	−4.116	4.89E-05	0.0298	−1.108	ARHGEF1	CAPS
−0.002	−0.188	−4.086	5.52E-05	0.0321	−1.224	RPL19	CAPS
−0.002	−0.147	−4.049	6.43E-05	0.0338	−1.369	AES	CAPS
−0.002	−0.173	−4.052	6.36E-05	0.0338	−1.358	GNAI2	CAPS
−0.002	−0.098	−4.033	6.86E-05	0.0338	−1.430	SPG7	CAPS
−0.002	−0.185	−4.031	6.92E-05	0.0338	−1.439	CLIC1	CAPS
−0.002	−0.169	−4.018	7.31E-05	0.0343	−1.490	GNB2	CAPS
−0.002	−0.194	−3.966	8.98E-05	0.0406	−1.686	ARPC3	CAPS
−0.002	−0.170	−3.937	0.000101	0.0424	−1.796	ENO1	CAPS
−0.002	−0.171	−3.939	0.000100	0.0424	−1.788	CD53	CAPS
−0.004	−0.175	−3.891	0.000121	0.0493	−1.970	IFITM1	CAPS
−0.002	−0.167	−3.881	0.000126	0.0495	−2.006	ARF1	CAPS
−0.009	−0.149	−4.594	6.24E-06	0.0254	2.260	COPE	Re-experiencing
−0.011	−0.174	−4.669	4.43E-06	0.0254	2.589	UBC	Re-experiencing
−0.008	−0.177	−4.682	4.18E-06	0.0254	2.646	FMNL1	Re-experiencing
−0.008	−0.177	−5.410	1.22E-07	0.0015	5.975	FMNL1	Dysphoric arousal
−0.009	−0.149	−5.158	4.36E-07	0.0027	4.744	COPE	Dysphoric arousal
−0.009	−0.169	−4.955	1.17E-06	0.0030	3.792	STXBP2	Dysphoric arousal
−0.009	−0.157	−4.962	1.12E-06	0.0030	3.827	UNC13D	Dysphoric arousal
−0.007	−0.157	−4.945	1.22E-06	0.0030	3.745	EIF4A1	Dysphoric arousal
−0.007	−0.169	−4.825	2.16E-06	0.0044	3.198	RPS6KA1	Dysphoric arousal
−0.009	−0.180	−4.378	1.62E-05	0.0179	1.264	RPL6	Dysphoric arousal
−0.009	−0.178	−4.407	1.43E-05	0.0179	1.385	PSME1	Dysphoric arousal
−0.009	−0.183	−4.397	1.49E-05	0.0179	1.343	LIMD2	Dysphoric arousal

Table 5. continued

b. Past-month CAPS score

Log2 fold-change	Average expression	t-statistic	P value	Adjusted P value	Beta coefficient	Gene symbol	Phenotype
−0.008	−0.171	−4.382	1.59E-05	0.0179	1.281	PTMA	Dysphoric arousal
−0.008	−0.181	−4.455	1.15E-05	0.0179	1.586	NACA	Dysphoric arousal
−0.010	−0.148	−4.280	2.47E-05	0.0251	0.860	GSTK1	Dysphoric arousal
−0.011	−0.204	−4.246	2.84E-05	0.0267	0.724	MYL6	Dysphoric arousal
−0.010	−0.184	−4.208	3.34E-05	0.0291	0.571	ABTB1	Dysphoric arousal
−0.008	−0.129	−4.181	3.74E-05	0.0304	0.464	DCAF11	Dysphoric arousal
−0.009	−0.190	−4.132	4.58E-05	0.0339	0.271	ALDOA	Dysphoric arousal
−0.007	−0.182	−4.124	4.73E-05	0.0339	0.239	ARPC4	Dysphoric arousal
−0.009	−0.199	−4.063	6.07E-05	0.0411	0.003	ICAM3	Dysphoric arousal
−0.007	−0.170	−4.041	6.65E-05	0.0427	−0.084	ARHGEF1	Dysphoric arousal
−0.008	−0.147	−3.993	8.05E-05	0.0491	−0.266	AES	Dysphoric arousal
−0.016	−0.149	−5.581	5.03E-08	0.0006	7.336	COPE	Anxious arousal
−0.014	−0.177	−5.201	3.51E-07	0.0021	5.456	FMNL1	Anxious arousal
−0.016	−0.157	−5.115	5.38E-07	0.0022	5.041	UNC13D	Anxious arousal
−0.020	−0.153	−5.005	9.18E-07	0.0028	4.526	DEF6	Anxious arousal
−0.019	−0.183	−4.729	3.37E-06	0.0076	3.274	H3F3B	Anxious arousal
−0.015	−0.171	−4.706	3.74E-06	0.0076	3.174	PTMA	Anxious arousal
−0.014	−0.164	−4.483	1.02E-05	0.0155	2.213	PKM	Anxious arousal
−0.014	−0.170	−4.338	1.93E-05	0.0155	1.606	ENO1	Anxious arousal
−0.015	−0.180	−4.294	2.32E-05	0.0155	1.428	RPL6	Anxious arousal
−0.013	−0.179	−4.334	1.96E-05	0.0155	1.590	EEF1D	Anxious arousal
−0.015	−0.170	−4.368	1.69E-05	0.0155	1.731	PFN1	Anxious arousal
−0.016	−0.168	−4.272	2.55E-05	0.0155	1.340	MYL12B	Anxious arousal
−0.016	−0.172	−4.279	2.47E-05	0.0155	1.369	CCNI	Anxious arousal
−0.014	−0.183	−4.320	2.08E-05	0.0155	1.533	LIMD2	Anxious arousal
−0.012	−0.158	−4.303	2.23E-05	0.0155	1.466	CTDSP1	Anxious arousal
−0.012	−0.190	−4.374	1.65E-05	0.0155	1.755	ARPC2	Anxious arousal
−0.012	−0.114	−4.283	2.43E-05	0.0155	1.386	HNRNPF	Anxious arousal
−0.014	−0.169	−4.382	1.59E-05	0.0155	1.788	GNB2	Anxious arousal
−0.013	−0.181	−4.294	2.32E-05	0.0155	1.427	NACA	Anxious arousal
−0.022	−0.123	−4.320	2.07E-05	0.0155	1.536	ARID5A	Anxious arousal
−0.015	−0.141	−4.232	3.02E-05	0.0160	1.178	SBNO2	Anxious arousal
−0.011	−0.125	−4.221	3.16E-05	0.0160	1.135	PPP2R1A	Anxious arousal
−0.015	−0.152	−4.233	3.00E-05	0.0160	1.182	CCNDBP1	Anxious arousal
−0.012	−0.182	−4.224	3.12E-05	0.0160	1.145	ARPC4	Anxious arousal
−0.011	−0.091	−4.156	4.14E-05	0.0190	0.877	ZNF207	Anxious arousal
−0.017	−0.194	−4.159	4.09E-05	0.0190	0.887	CYBA	Anxious arousal
−0.013	−0.172	−4.152	4.21E-05	0.0190	0.861	WBP2	Anxious arousal
−0.012	−0.173	−4.113	4.94E-05	0.0212	0.708	GNAI2	Anxious arousal
−0.011	−0.157	−4.109	5.04E-05	0.0212	0.691	EIF4A1	Anxious arousal
−0.014	−0.190	−4.085	5.55E-05	0.0226	0.598	ALDOA	Anxious arousal
−0.012	−0.152	−4.022	7.17E-05	0.0267	0.356	SNRNP70	Anxious arousal
−0.011	−0.169	−4.006	7.66E-05	0.0267	0.293	RPS6KA1	Anxious arousal
−0.013	−0.109	−4.021	7.22E-05	0.0267	0.349	NDUFV1	Anxious arousal
−0.015	−0.166	−4.009	7.56E-05	0.0267	0.306	C17orf62	Anxious arousal
−0.016	−0.146	−4.026	7.08E-05	0.0267	0.368	CASP4	Anxious arousal
−0.013	−0.150	−3.994	8.05E-05	0.0273	0.246	PPP4C	Anxious arousal
−0.015	−0.179	−3.962	9.16E-05	0.0299	0.124	CNPY3	Anxious arousal
−0.010	−0.146	−3.948	9.66E-05	0.0299	0.073	PSMB4	Anxious arousal
−0.021	−0.172	−3.953	9.46E-05	0.0299	0.093	RPL8	Anxious arousal

Table 5. continued

b. Past-month CAPS score

Log2 fold-change	Average expression	t-statistic	P value	Adjusted P value	Beta coefficient	Gene symbol	Phenotype
−0.014	−0.159	−3.944	9.82E-05	0.0299	0.058	PCBP1	Anxious arousal
−0.014	−0.130	−3.917	0.000109	0.0325	−0.043	NADSYN1	Anxious arousal
−0.020	−0.149	−3.895	0.000119	0.0338	−0.126	JAK3	Anxious arousal
−0.011	−0.160	−3.897	0.000118	0.0338	−0.118	ARAP1	Anxious arousal
−0.013	−0.167	−3.878	0.000128	0.0342	−0.190	ATP2A3	Anxious arousal
−0.010	−0.161	−3.862	0.000136	0.0342	−0.248	RAB7A	Anxious arousal
−0.012	−0.169	−3.863	0.000135	0.0342	−0.244	STXBP2	Anxious arousal
−0.011	−0.169	−3.885	0.000124	0.0342	−0.162	HNRNPC	Anxious arousal
−0.015	−0.184	−3.860	0.000137	0.0342	−0.255	ABTB1	Anxious arousal
−0.014	−0.098	−3.859	0.000137	0.0342	−0.259	SPG7	Anxious arousal
−0.014	−0.189	−3.843	0.000146	0.0349	−0.318	MYL12A	Anxious arousal
−0.012	−0.064	−3.843	0.000146	0.0349	−0.316	HP1BP3	Anxious arousal
−0.017	−0.204	−3.833	0.000152	0.0356	−0.355	MYL6	Anxious arousal
−0.010	−0.175	−3.802	0.000171	0.0380	−0.467	RHOA	Anxious arousal
−0.013	−0.095	−3.807	0.000168	0.0380	−0.448	XAB2	Anxious arousal
−0.013	−0.117	−3.804	0.000170	0.0380	−0.459	PTPRC	Anxious arousal
−0.011	−0.148	−3.796	0.000176	0.0383	−0.491	CDC37	Anxious arousal
−0.010	−0.138	−3.774	0.000191	0.0409	−0.571	STAT3	Anxious arousal
−0.009	−0.161	−3.744	0.000214	0.0450	−0.678	HNRNPK	Anxious arousal
−0.011	−0.164	−3.737	0.000220	0.0454	−0.701	LRCH4	Anxious arousal
−0.011	−0.152	−3.728	0.000228	0.0456	−0.737	HNRNPA2B1	Anxious arousal
−0.013	−0.162	−3.729	0.000227	0.0456	−0.732	SIPA1	Anxious arousal
−0.007	−0.149	−4.937	1.27E-06	0.0155	3.495	COPE	Numbing
−0.007	−0.157	−4.662	4.58E-06	0.0279	2.260	UNC13D	Numbing
−0.006	−0.169	−4.491	9.87E-06	0.0386	1.524	RPS6KA1	Numbing
−0.006	−0.181	−4.434	1.27E-05	0.0386	1.284	NACA	Numbing
−0.014	−0.149	−4.888	1.60E-06	0.0131	3.967	COPE	Avoidance
−0.019	−0.138	−4.825	2.15E-06	0.0131	3.684	FURIN	Avoidance
−0.012	−0.177	−4.514	8.92E-06	0.0363	2.320	FMNL1	Avoidance

number of genes (61 and 82, respectively; Table 5) associated with anxious arousal, including many genes not associated with any other phenotype in our analysis (16, 27, respectively). By contrast, although we identified a substantial number of genes significantly associated with dysphoric arousal (20, 16 for past-month and lifetime respectively), only two genes were uniquely associated with this phenotype (1 gene in past-month; 2 in lifetime). Only one gene, *COPE*, was significantly associated with every phenotype tested in our analysis. A second gene, *EIF4A1*, was also significantly associated with every lifetime (highest) phenotype (Fig. 4).

PTSD pathway enrichment demonstrates immune, psychiatric, and metabolic relationships

Our genetic enrichment and pathway analyses identified well-established PTSD mechanisms and pathways, including pathways associated with inflammation, neurological signaling pathways, structural remodeling within and between cells, and HPA-axis and signaling [53–58]. Based on our KEGG pathway enrichment analysis, we revealed a set of genes significantly associated (FDR $p < 0.05$) with psychiatric disorders pathways that were significantly enriched in our results: *FURIN, PPP2R1A, GNAI2, PCLB2*, and *GNB2*. The two symptom dimensions that we discovered were associated with *FURIN* and their FDR-corrected p values were avoidance ($p = 0.028$, $B = 2.55$) and numbing ($p = 0.034$, $B = -0.009$). *PPP2R1A* was associated with anxious arousal ($p = 0.009$, $B = 2.60$). *PCLB2* was only associated with numbing ($p = 0.046$, $B = -0.952$). *GNAI2* was associated with anxious arousal ($p = 0.042$, $B = -0.780$) and numbing ($p = 0.047$, $B = -1.03$), and *GNB2* was only associated with avoidance ($p = 0.036$, $B = 1.130$) (Fig. 5).

Immunological and metabolic gene enrichment was consistent across lifetime CAPS score and numbing, but was less pronounced in anxious arousal. For past-month analyses, immune function was most associated with anxious arousal, whereas metabolic function was enriched in past-month CAPS, and numbing, to a lesser extent. For both lifetime and past-month scores, neurological signaling pathways were most significantly pronounced in numbing, and were less prevalent in the overall total CAPS score analysis. For lifetime scores, structural pathway enrichment was significantly higher in total CAPS score, anxious arousal, and numbing, whereas for past-month scores, structural enrichment was most associated with anxious arousal (Fig. 5).

Meta-analysis prioritizes 10 genes associated with PTSD

We sought to replicate our associations with previous PTSD studies. Since the majority of publicly available PTSD gene expression analyses follow a case-control, rather than quantitative measure (CAPS score) analysis, we converted our continuous past-month CAPS and lifetime CAPS values to PTSD case/control using CAPS ≥ 40 and DSM-IV PTSD-criteria, and repeated our analysis. Our case/control and CAPS score association statistics were

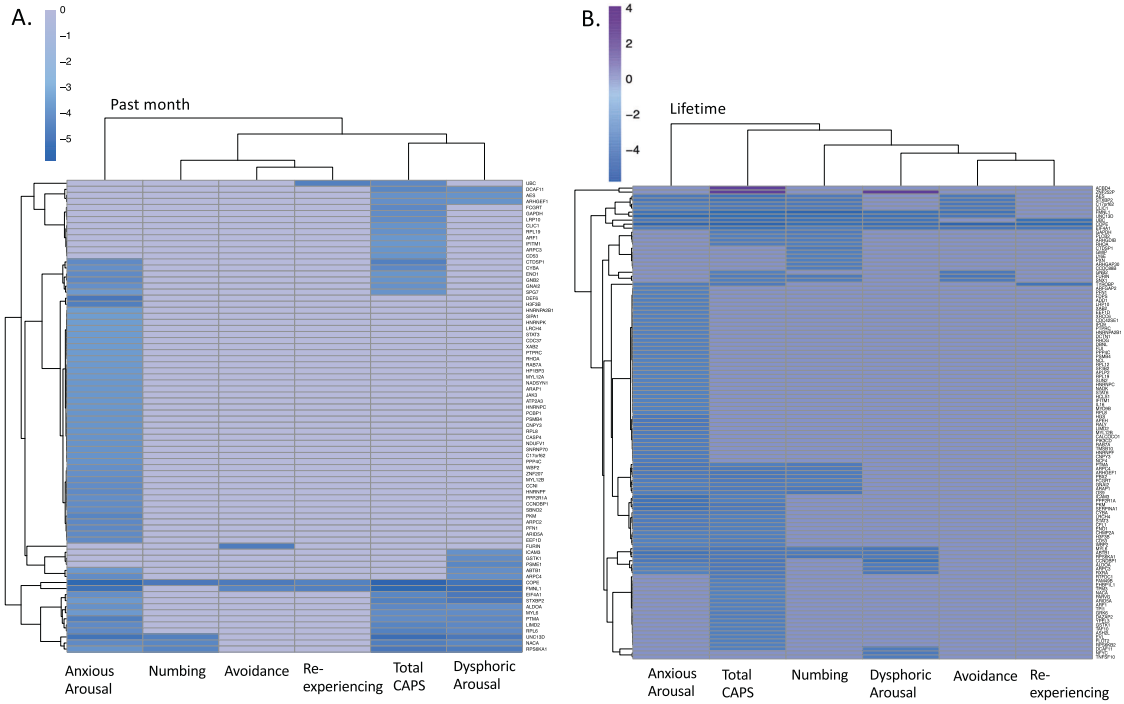

Fig. 4 Heatmap of differentially expressed ($p < 0.05$) genes from a gene expression analysis across past-month Clinician-Administered PTSD Scale (CAPS) and symptom dimensions and lifetime CAPS and symptom dimensions in $N = 355$ World Trade Center first-responders. Phenotypes were corrected for sex, age, batch, and first 10 ancestry principal components. Gene clusters represent genealogical expression diversity among (**A**) past-month CAPS and symptom dimensions and (**B**) lifetime CAPS and symptom dimensions.

significantly correlated ($\rho = 0.72$, $p < 2.2 \times 10^{-16}$, $\rho = 0.79$, $p < 2.2 \times 10^{-16}$); however, we note a substantial decrease in the number of significantly associated genes when using a case-control design, compared to our initial quantitative analysis, as we would expect [17]. Twelve genes were significant for past-month PTSD ($PTSD_{PM}$) case/control and 22 genes were significant for lifetime PTSD ($PTSD_L$) case/control, versus 31 genes for past-month CAPS score and 66 genes for lifetime CAPS score.

We meta-analyzed our results with five publicly available cohorts ($N = 739$ cases, 438 controls); two including WTC responders, and three including combat and interpersonal trauma (Table 2). For $PTSD_{PM}$ we identified 5 significant genes –*COPE, CIRBP, FCGRT, NACA*, and *ZNF429* ($p < 5.33 \times 10^{-6}$)–, and for $PTSD_L$ 8 significant genes –*COPE*, *CIRBP, TMSB10, FCGRT, CLIC1, RPS6KB2, HNRNPUL1* and *ALDOA* ($p < 4.92 \times 10^{-5}$)–, including genes associated with inflammation and immune response (Fig. 6). Of these 10 genes, only one (*COPE*) had significant heterogeneity of effect size between cohorts: our study and TMA-combat. Three further genes were unique to our study; *NACA* $p = 3.34 \times 10^{-6}$, *CLIC1*, $p = 1.9 \times 10^{-5}$, and *HNRNPUL1* $p = 4.08 \times 10^{-5}$ (Fig. 6). The remaining six genes were significant across multiple studies in our meta-analysis, with highly consistent (negative) direction of effect (i.e., consistently decreased expression in cases compared to controls): *ZNF439* ($p = 4.78 \times 10^{-6}$), *CIRBP* ($p = 1.29 \times 10^{-6}$), *TMSB10* ($p = 6.31 \times 10^{-6}$), *FCGRT* ($p = 1.12 \times 10^{-5}$), *RPS6KB2* ($p = 3.47 \times 10^{-5}$), and *ALDOA* ($p = 4.66 \times 10^{-5}$) (Table 6).

Cellular deconvolution identifies differences in cell populations between responders with PTSD and controls

Since many of our PTSD-associated genes are related to immune function, we tested whether immune cell type proportions were correlated with CAPS scores in individuals in our sample. We performed cell-type deconvolution to identify cell-type proportions for 22 cell types across all 355 individuals in our sample. We found significant increase of CD4 naïve T cell ($p < 0.0049$) proportions with past-month CAPS, and significant increase of eosinophils ($p < 0.042$) and CD4 memory resting T cells ($p < 0.044$) associated with lifetime CAPS. In addition, we found significant decrease of activated natural killer cells ($p < 0.040$) associated with lifetime CAPS. (Fig. 7).

DISCUSSION

Although trauma is ubiquitous as a human experience, the types of traumatic experiences vary greatly among individuals. Our study sample and design present a unique opportunity to examine gene expression and PTSD symptoms related to a particular traumatic experience, the 9/11 WTC disaster and its aftermath. To our knowledge, ours is the largest single-traumatic event gene expression dataset to date. Using CAPS score as a quantitative measure of WTC-related PTSD symptom severity, we found 66 genes associated with lifetime (highest) CAPS score and 31 genes associated with past-month CAPS score. We additionally found interaction between lifetime CAPS and one gene, *STX10*, in medical comorbidities. Pathway analysis links our associated genes to metabolic, immunological, structural, and neurological pathways. In addition, we found 10 genes associated with lifetime and past-month PTSD: *COPE, CIRBP*, and *FCGRT* shared between the two; *NACA* and *ZNF429* specific to past-month PTSD; and *TMSB10*, *CLIC1, RPS6KB2, HNRNPUL1* and *ALDOA* specific to lifetime PTSD. Furthermore, cellular analysis of our cohort demonstrated an enrichment in CD4 T cells and eosinophils in responders with PTSD. Additionally, natural killer cells were decreased in these patients. Our findings support previous studies, which tie together the immune system and PTSD as a systemic disease. Ultimately, these results represent an additional wealth of knowledge to help understand the genetic expression and biological etiology of PTSD, and uncover potential biomarkers for the disease.

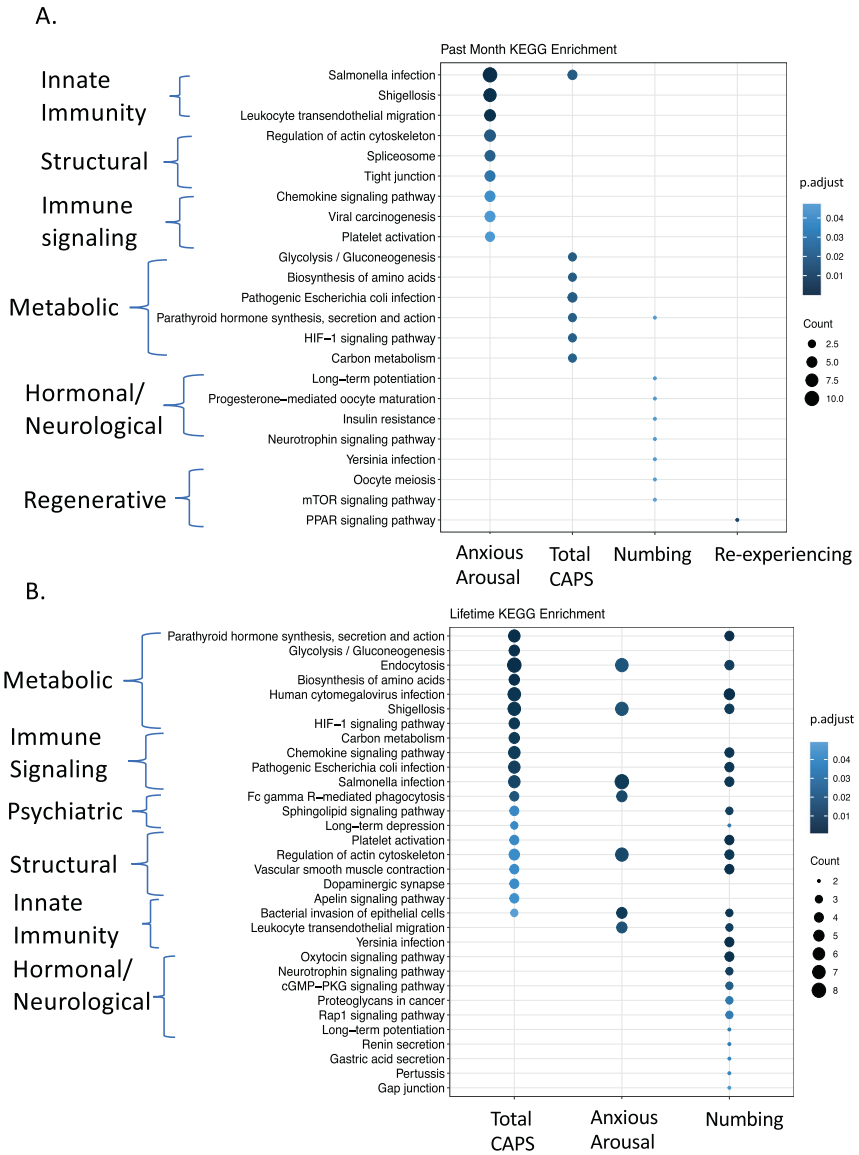

Fig. 5 KEGG pathway enrichment of differentially expressed genes in $N = 355$ World Trade Center first-responders in past-month and lifetime Clinician-Administered PTSD Scale (CAPS). Pathways categorically grouped by metabolic, immune signaling, innate immunity, structural, hormonal/neurological, regenerative and psychiatric function in (**A**) past-month CAPS and (**B**) lifetime CAPS.

Examining both lifetime and past-month CAPS scores allowed us to look at not only chronic effects of PTSD but longevity of the outcomes. While past-month CAPS is considered the standard for case/control analysis, looking at both lifetime CAPS and past-month CAPS allows us to ask more specific questions about the role and relevance of elevated gene expression in PTSD. For example, genes associated with past-month CAPS might represent current expression changes in PTSD, while those associated with lifetime CAPS (lifetime CAPS score representing, for each responder, the highest WTC-related PTSD symptom levels ever reached since 9/11/2011) may represent long-lasting expression changes resulting from lifetime PTSD.

We identified genes associated with past-month and lifetime CAPS scores that have been associated with other psychiatric disorders, such as major depressive disorder, schizophrenia and autism: *FURIN, PPP2R1A, PLCB2, GNAI2, and GNB2* (Fig. 6) [51, 59–70]. We additionally identified a group of genes as significantly associated with several lifetime and past-month PTSD symptom dimensions (*SERPINA1, RPS6KA1*, and *STAT3*) that have been previously linked to PTSD pathophysiology [1, 27–31, and genes associated specifically with anxious arousal that have been previously associated with anxiety disorders: *DCTN1*, and *FLI1* [71, 72]. One gene in our study, *COPE*, was associated with every PTSD phenotype in this analysis.

Until now, *COPE* has not been well studied in the context of psychiatric disorders [73], but it has been implicated in the context of Alzheimer's disease [74, 75]. Canonically, the COPE protein is the epsilon subunit of the coatomer protein complex I (COPI) which regulates endocytosis from the plasma membrane and is involved in Golgi-to-lysosome transportation. Aberrant autophagy via the Golgi has been linked to many neurological disorders [76]. Other subunits of COPI have been implicated in hereditary diseases that cause microcephaly and in autoimmune disorders [77–79]. Additionally, *DCTN1*, *FURIN* and possibly *SERPINA1* all might play a role in the dysregulation of Golgi-lysosomal pathway, which further highlights the potential of this pathway in etiology of PTSD. The strong significance of *COPE* and other genes found in this study warrants further investigation

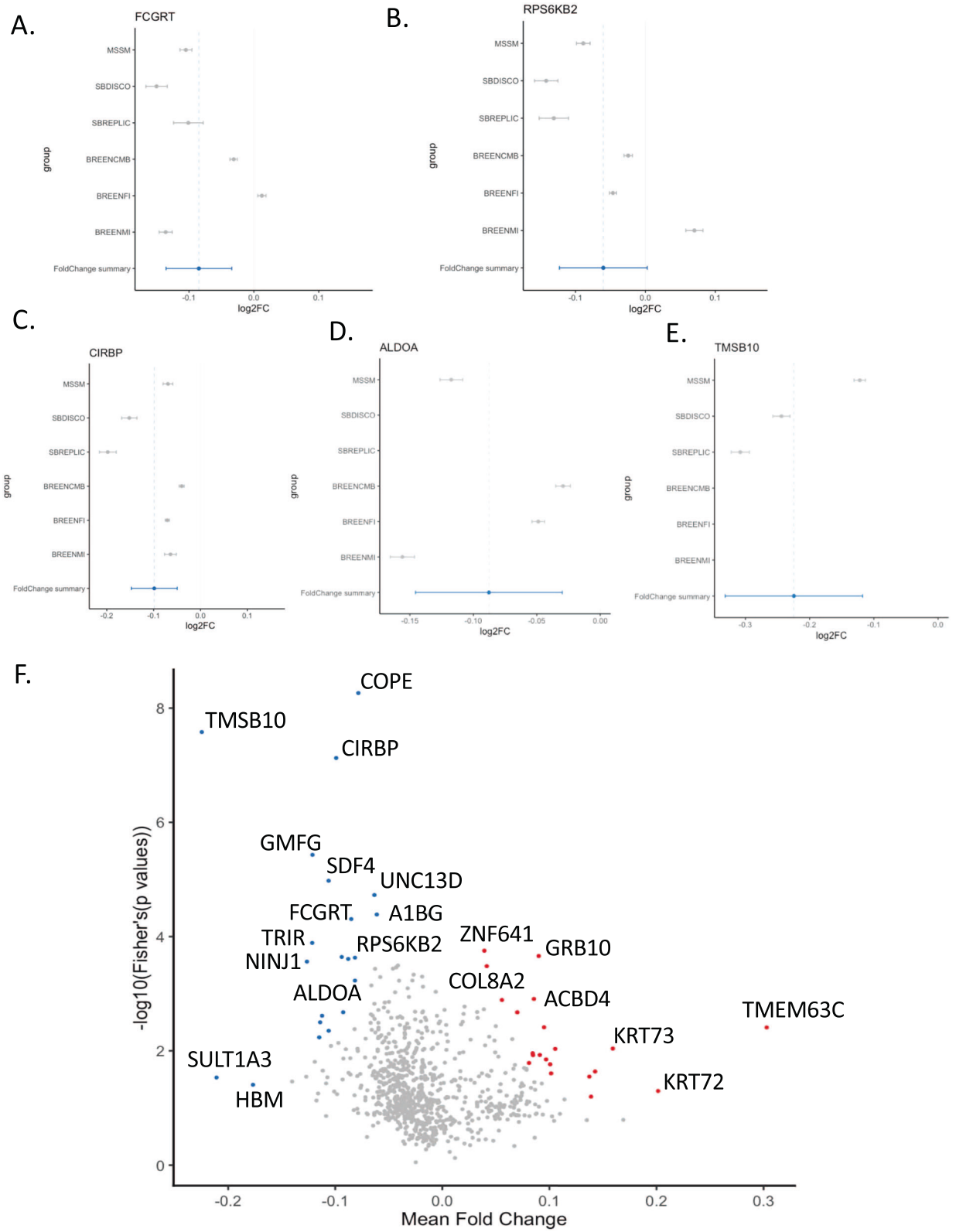

Fig. 6 Forestplots and volcano plot of genome-wide significant genes from our meta-analysis. Meta-analysis included our gene expression analysis, another World Trade Center (WTC) study, and a mega-analysis of 8 different compiled trauma studies. Genome-wide significant gene forestplots include: (**A**) FCGRT, (**B**) RPS6KB2, (**C**) CIRBP, (**D**) ALDOA, and (**E**) TMSB10. (**F**) Volcano plot of genome-wide significant genes.

Table 6. Meta-analysis of study results with five publicly available cohorts.

Lifetime PTSD								
Marker name	**Weight**	**Z-score**	***P* value**	**Direction**	**Heterogenous I-squared**	**Heterogenous Chi-squared**	**Heterogenous degrees of freedom**	**Heterogenous *P* value**
COPE	524	−5.277	1.31E-07	−??−??	91.7	12.103	1	0.0005034
CIRBP	982	−4.842	1.29E-06	−−?−−−	0	3.785	4	0.4358
TMSB10	442	−4.516	6.31E-06	−−????	32	1.47	1	0.2253
FCGRT	1177	−4.392	1.12E-05	−−−−+−	52	10.423	5	0.06411
ALDOA	895	−4.072	4.66E-05	−??−−−	43.2	5.281	3	0.1523
RPS6KB2	1177	−4.14	3.47E-05	−−−−−+	50.5	10.099	5	0.07248
HNRNPUL1	355	−4.103	4.08E-05	−?????	0	0	0	1
CLIC1	355	−4.276	1.90E-05	−?????	0	0	0	1
Past-month PTSD								
Marker name	Weight	Z-score	*P* value	Direction	Heterogenous I-squared	Heterogenous Chi-squared	Heterogenous degrees of freedom	Heterogenous *P* value
COPE	524	−4.778	1.77E-06	−??−??	89.8	9.826	1	0.00172
CIRBP	982	−5.016	5.27E-07	−−?−−−	0	3.676	4	0.4516
FCGRT	1177	−4.793	1.64E-06	−−−−−+	59.9	12.475	5	0.02883
ZNF439	451	−4.574	4.78E-06	?−−−??	0	1.695	2	0.4285
NACA	355	−4.649	3.34E-06	−?????	0	0	0	1

Direction is defined as our study, WTC discovery cohort [3], WTC replication cohort [3], military trauma, male interpersonal trauma and female interpersonal trauma (from mega-analysis study [10]).
CAPS-5 Clinician-Administered PTSD Scale.

into PTSD, autophagy and the Golgi-to-lysosome transportation pathway.

In addition to Golgi processing, a few of our significant genes are also involved in beta- and alpha-adrenergic signaling pathways: *PPP2R1A, EIF4A1, GNAI2*, and *GNB2*. A hyper-noradrenergic state has previously been implicated in PTSD etiology [80]. As such, propranolol, a beta-adrenergic receptor blocker, has been tested and had measured success as a fear-reducing agent in the treatment of PTSD pathophysiology [81]. The significance of the genes found in this study further highlight the role of alpha- and beta-adrenergic signaling pathways in PTSD etiology and suggest that drugs involved in these pathways may have beneficial effects towards PTSD treatment.

Importantly, our analytical design allowed us to test for potential confounding effects of comorbidities and environmental exposures [82, 83]. We expected many of these comorbidities and exposures to have a significant impact on gene expression, particularly as some comorbidities may be more recently occurring than, for example, the highest lifetime CAPS measure. Therefore, we tested directly for genes associated with (i) comorbidities and (ii) dust cloud exposure. Although we identified a large number of genes associated with each phenotype, we note that our associations do not overlap with our top PTSD genes; we did not observe significant enrichment of shared associations, and only observed one gene with significant interaction effect between comorbidities and lifetime CAPS. Therefore, we conclude that our results are not confounded by these exposures; our gene associations are specific to PTSD rather than broadly corresponding to exposure or general ill health.

KEGG enrichment of our associated genes determined genetic changes in metabolic, immunological, structural, and neurological pathways associated with total CAPS, numbing, and anxious arousal phenotypes (Fig. 7). Anxious arousal and numbing tend to have few significantly associated genes in common, while both past-month and lifetime CAPS scores display a few unique genes but many shared ones. *GNAI2*, while associated with many numbing-related pathways (long-term depression, oxytocin signaling, etc.), is also significantly associated with some peripheral anxious arousal-related and lifetime CAPS–related pathways (leukocyte migration, and chemokine signaling, respectively). On the other hand, anxious arousal is uniquely associated with genes such as *HGS, ARFGAP2* and *RAB7A*, which are linked to endocytosis and immunity. Similarly, our past-month and lifetime CAPS phenotypes are uniquely associated with glycolysis/gluconeogenesis for genes *ALDOA, GAPDH, ENO1, TPI1*, and *PKM*, which may play roles in HPA-axis or metabolic dysregulation (Table 4).

Our analyses identified 10 genes reaching genome-wide significance. Of these, 3/10 (*NACA* $p = 3.34 \times 10^{-6}$, *CLIC1*, $p = 1.9 \times 10^{-5}$, and *HNRNPUL1* $p = 4.08 \times 10^{-5}$) are specific to our study; all three are downregulated in WTC responders with PTSD compared to controls. *NACA* has been previously studied as a potential biomarker for depression in mice under stress conditions [84]. The function of *HNRNPUL1* is relatively unknown. Studies have suggested it might play a role in DNA damage repair and nucleocytoplasmic RNA transport. *CLIC1* has been implicated in other psychiatric disorders, but its primary function is inflammasome regulation [85–87]. In addition, 6/10 genes had highly consistent directions of effect. These include *FCGRT* ($p = 1.12 \times 10^{-05}$), which has been characterized as an immune regulator of dendritic cell cross-presentation of IgG immune complexes, necessary to activate a cytotoxic T-cell response and clear antigens [88]. Our analysis demonstrates a downregulation of *FCGRT* in WTC responders with PTSD, suggesting reduced IgG immune complex clearance in these patients (Fig. 6).

There is evidence that macro- and micro-level physiological damage is a fundamental component of PTSD, as well as cytoskeletal restructuring for fear-based memory formation in the amygdala [57, 58]. In this study we observed decreased expression in *CIRBP* ($p = 1.29 \times 10^{-06}$), a protein that traditionally regulates stress and apoptosis under conditions of extreme cold (Fig. 6). Its role as a potential biomarker has been previously explored for different psychiatric disorders [89, 90]. The decrease

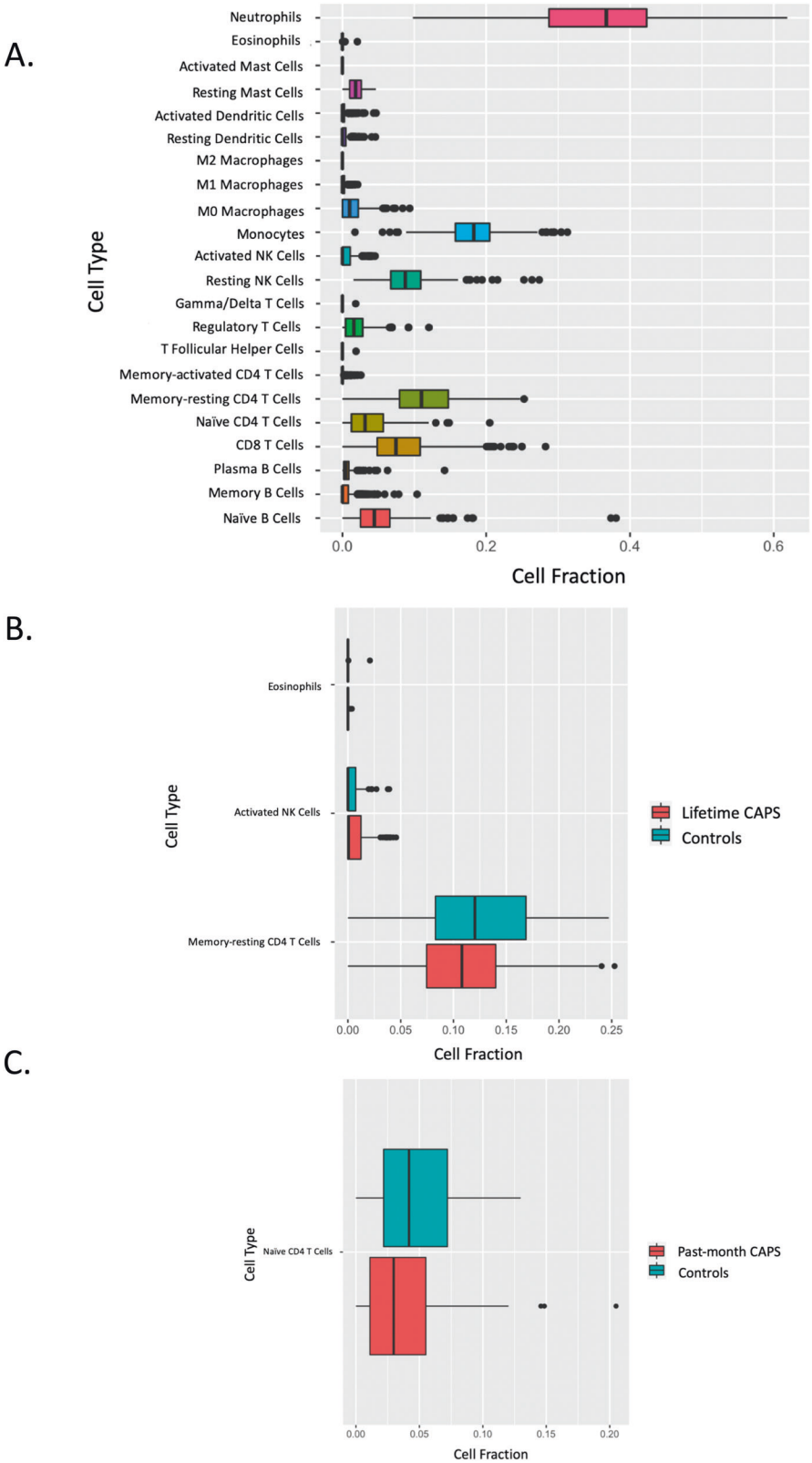

Fig. 7 Cellular deconvolution of immune cells in peripheral blood; significant cell type differences for Clinician-Administered PTSD Scale (CAPS) lifetime and past-month compared to controls are noted. A Immune cell composition of overall sample, and comparison of significantly different cellular fractions of CAPS (>40) versus controls (<40) in (**B**) lifetime CAPS and (**C**) past-month CAPS.

observed in *TMSB10* expression also contributes to the dysregulation of apoptosis. *TMSB10* is a pro-apoptotic protein that has been previously associated with downregulation of gene expression after trauma exposure [3, 91, 92]. In our meta-analysis, the directionality of effect ($p < 2.2 \times 10^{-16}$) for each gene was decreased, consistent with PTSD pathophysiology [93, 94].

Since many of our PTSD-associated genes are related to immune function, we tested for the enrichment of immune cell types in our study. We found an overall enrichment of CD4-positive T cells for both past-month and lifetime CAPS scores (Fig. 7), consistent with previous studies [95, 96], including among WTC responders [6]. In addition to CD4 T cell enrichment, our study also found enrichment in eosinophils and a decrease in natural killer cells for lifetime CAPS (Fig. 7). These cellular diversities may point to a higher inflammatory signature in PTSD, particularly in the case of CD4 T cell enrichment. It has been well demonstrated that dysregulation of CD4 T cells leads to autoimmune activation [97], and in combination with an increase in eosinophils can lead to an inflammatory cascade in patients. There is strong evidence that PTSD is associated with a pro-inflammatory state, which our findings support [98–102].

While our study provides an in-depth look at the genetic expression and outcomes related to a specific traumatic experience, we note some significant caveats. Our expression analysis was limited to blood, but should be expanded to other tissues in the future, such as the post-mortem brain. Similarly, our analysis was restricted to whole blood, but a more in-depth single cell analysis will be critical to determine gene expression in individual cell types. In addition, we note that our cohort includes a significant proportion of individuals who have self-selected into high-risk professions. As such, we expect a higher lifetime exposure to stressful situations, including potentially many other life-threatening scenarios. It is likely that the PTSD symptoms observed here are at least partially accounted for by other traumas and stressors, even though upon CAPS administration, study clinicians specifically inquired about WTC-related PTSD symptoms. Conversely, the high-risk nature of these individuals' occupations may also mean increased exposure to resilience training for a sizable subsample, and greater access to social support networks of peers with similar experiences, potentially providing protective mechanisms.

In conclusion, this study has identified a vast number of biomarkers that will be potentially useful tools after independent validation. In particular, ten of these genes stand out as reproducible across multiple studies and should be considered as high priority. In combination with pathway and cellular deconvolution results, these findings highlight a strong connection with immune dysregulation and other psychiatric illnesses. We believe that future studies should focus on validation of our PTSD-associated genes and also single-cell RNA-sequencing approaches to delineate the role of immune cell types in PTSD.

CODE AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

REFERENCES

1. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV axis I disorders, clinician version (SCID-CV). New York: Biometrics Research, New York State Psychiatric Institute; 2002.
2. Yehuda R, Cai G, Golier JA, Sarapas C, Galea S, Ising M, et al. Gene expression patterns associated with posttraumatic stress disorder following exposure to the World Trade Center attacks. Biol Psychiatry. 2009;66:708–11.
3. Kuan P-F, Waszczuk MA, Kotov R, Clouston S, Yang X, Singh PK, et al. Gene expression associated with PTSD in World Trade Center responders: an RNA sequencing study. Transl Psychiatry. 2017;7:1297.
4. Clouston S, Pietrzak RH, Kotov R, Richards M, Spiro A, Scott S, et al. Traumatic exposures, posttraumatic stress disorder, and cognitive functioning in World Trade Center responders. Alzheimers Dement N. Y N. 2017;3:593–602.
5. Gong Y, Wang L, Yu H, Alpert N, Cohen MD, Prophete C, et al. Prostate cancer in World Trade Center responders demonstrates evidence of an inflammatory cascade. Mol Cancer Res. 2019;17:1605–12.
6. Kuan P-F, Yang X, Clouston S, Ren X, Kotov R, Waszczuk M, et al. Cell type-specific gene expression patterns associated with posttraumatic stress disorder in World Trade Center responders. Transl Psychiatry. 2019;9:1–11.
7. Kuan P-F, Mi Z, Georgopoulos P, Hashim D, Luft B, Boffetta P. Enhanced exposure assessment and genome-wide DNA methylation in World Trade Center disaster responders. Eur J Cancer Prev. 2019;28:225–33.
8. Sarapas C, Cai G, Bierer LM, Golier JA, Galea S, Ising M, et al. Genetic markers for PTSD risk and resilience among survivors of the World Trade Center attacks. Dis Markers. 2011;30:101–10.
9. Huckins LM, Chatzinakos C, Breen MS, Hartmann J, Klengel T, Almeida AC, et al. Analysis of genetically regulated gene expression identifies a trauma type specific PTSD gene, SNRNP35, Specific to Military Cohorts. Cell Rep. 2020;31:107716.
10. Breen MS, Tylee DS, Maihofer AX, Neylan TC, Mehta D, Binder EB, et al. PTSD blood transcriptome mega-analysis: shared inflammatory pathways across biological sex and modes of trauma. Neuropsychopharmacology 2018;43:469–81.
11. Pietrzak RH, Tsai J, Harpaz-Rotem I, Whealin JM, Southwick SM. Support for a novel five-factor model of posttraumatic stress symptoms in three independent samples of Iraq/Afghanistan veterans: a confirmatory factor analytic study. J Psychiatr Res. 2012;46:317–22.
12. Mar JC. The rise of the distributions: why non-normality is important for understanding the transcriptome and beyond. Biophys Rev. 2019;11:89–94.
13. de Torrenté L, Zimmerman S, Suzuki M, Christopeit M, Greally JM, Mar JC. The shape of gene expression distributions matter: how incorporating distribution shape improves the interpretation of cancer transcriptomic data. BMC Bioinforma. 2020;21:562.
14. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, et al. The development of a clinician-administered PTSD scale. J Trauma Stress. 1995;8:75–90.
15. Fanous AH, Kendler KS. Genetic heterogeneity, modifier genes, and quantitative phenotypes in psychiatric illness: searching for a framework. Mol Psychiatry. 2005;10:6–13.
16. Schijven D, Geuze E, Vinkers CH, Pulit SL, Schür RR, Malgaz M, et al. Multivariate genome-wide analysis of stress-related quantitative phenotypes. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. 2019;29:1354–64.
17. Lee SH, Wray NR. Novel genetic analysis for case-control genome-wide association studies: quantification of power and genomic prediction accuracy. PLoS ONE. 2013;8:e71494.
18. Horn SR, Pietrzak RH, Schechter C, Bromet EJ, Katz CL, Reissman DB, et al. Latent typologies of posttraumatic stress disorder in World Trade Center responders. J Psychiatr Res. 2016;83:151–159.
19. Pietrzak RH, Feder A, Schechter CB, Singh R, Cancelmo L, Bromet EJ, et al. Dimensional structure and course of post-traumatic stress symptomatology in World Trade Center responders. Psychol Med. 2014;44:2085–98.
20. Dasaro CR, Holden WL, Berman KD, Crane MA, Kaplan JR, Lucchini RG, et al. Cohort profile: World Trade Center health program general responder cohort. Int J Epidemiol. 2017;46:e9.
21. Ruggiero KJ, Del Ben K, Scotti JR, Rabalais AE. Psychometric properties of the PTSD Checklist-Civilian Version. J Trauma Stress. 2003;16:495–502.
22. Huckins LM, Johnson JS, Cancelmo L, Diab O, Schaffer J, Cahn L, et al. Polygenic regulation of PTSD severity and outcomes among World Trade Center responders. MedRxiv. 2020. https://www.medrxiv.org/content/10.1101/2020.12.06.20244772v1.
23. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abus Negl. 2003;27:169–90.
24. Kubany ES, Haynes SN, Leisen MB, Owens JA, Kaplan AS, Watson SB, et al. Development and preliminary validation of a brief broad-spectrum measure of trauma exposure: the Traumatic Life Events Questionnaire. Psychol Assess. 2000;12:210–24.
25. Robins L, Cottler L, Bucholz K, Compton W, North C, Rourke K. The Diagnostic Interview Schedule for DSM-IV (DIS-IV) St. Louis, MO: Washington University; 1999.
26. Pietrzak RH, Goldstein RB, Southwick SM, Grant BF. Medical comorbidity of full and partial posttraumatic stress disorder in US adults: results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. Psychosom Med. 2011;73:697–707.
27. Hardik Shah Y.-C.W., Rafael Castellanos, Chetanya Pandya, Zachary Giles, RAPiD: An Agile and Dependable RNA-Seq Framework. The 65th Annual Meeting of The American Society of Human Genetics, 2015.

28. Hoffman GE, Schadt EE. variancePartition: interpreting drivers of variation in complex gene expression studies. BMC Bioinforma. 2016;17:483.
29. Law CW, Chen Y, Shi W, Smyth GK. voom: precision weights unlock linear model analysis tools for RNA-seq read counts. Genome Biol. 2014;15:R29.
30. Leek JT, Johnson WE, Parker HS, Jaffe AE, Storey JD. The sva package for removing batch effects and other unwanted variation in high-throughput experiments. Bioinformatics. 2012;28:882–883.
31. Mellon SH, Gautam A, Hammamieh R, Jett M, Wolkowitz OM. Metabolism, metabolomics, and inflammation in posttraumatic stress disorder. Biol Psychiatry. 2018;83:866–75.
32. Luft BJ, Schechter C, Kotov R, Broihier J, Reissman D, Guerrera K, et al. Exposure, probable PTSD and lower respiratory illness among World Trade Center rescue, recovery and clean-up workers. Psychol Med. 2012;42:1069–79.
33. Brackbill RM, Hadler JL, DiGrande L, Ekenga CC, Farfel MR, Friedman S, et al. Asthma and posttraumatic stress symptoms 5 to 6 years following exposure to the World Trade Center terrorist attack. JAMA. 2009;302:502–16.
34. Jordan HT, Miller-Archie SA, Cone JE, Morabia A, Stellman SD. Heart disease among adults exposed to the September 11, 2001 World Trade Center disaster: results from the World Trade Center Health Registry. Prev Med. 2011;53:370–376.
35. Feder A, Mota N, Salim R, Rodriguez J, Singh R, Schaffer J, et al. Risk, coping and PTSD symptom trajectories in World Trade Center responders. J Psychiatr Res. 2016;82:68–79.
36. Brackbill RM, Cone JE, Farfel MR, Stellman SD. Chronic physical health consequences of being injured during the terrorist attacks on World Trade Center on September 11, 2001. Am J Epidemiol. 2014;179:1076–85.
37. Wisnivesky JP, Teitelbaum SL, Todd AC, Boffetta P, Crane M, Crowley L, et al. Persistence of multiple illnesses in World Trade Center rescue and recovery workers: a cohort study. Lancet Lond Engl. 2011;378:888–97.
38. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B Methodol. 1995;57:289–300.
39. Bild A, Febbo PG. Application of a priori established gene sets to discover biologically important differential expression in microarray data. Proc Natl Acad Sci. 2005;102:15278–15279.
40. Korotkevich G, Sukhov V, Sergushichev A. Fast gene set enrichment analysis. BioRxiv. 2019. https://www.biorxiv.org/content/10.1101/060012v3.
41. How to do GSEA in R with (fgsea or gage) and plot results. Bioinforma Breakdown. 2019. https://bioinformaticsbreakdown.com/how-to-gsea/. Accessed 20 December 2019.
42. Kanehisa M, Sato Y, Kawashima M, Furumichi M, Tanabe M. KEGG as a reference resource for gene and protein annotation. Nucleic Acids Res. 2016;44:D457–D462.
43. Yu G, Wang L-G, Han Y, He Q-Y. clusterProfiler: an R package for comparing biological themes among gene clusters. OMICS J Integr Biol. 2012;16:284–287.
44. Mehta D, Klengel T, Conneely KN, Smith AK, Altmann A, Pace TW, et al. Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. Proc Natl Acad Sci. 2013;110:8302–8307.
45. Neylan TC, Sun B, Rempel H, Ross J, Lenoci M, O'Donovan A, et al. Suppressed monocyte gene expression profile in men versus women with PTSD. Brain Behav Immun. 2011;25:524–31.
46. Segman RH, Shefi N, Goltser-Dubner T, Friedman N, Kaminski N, Shalev AY. Peripheral blood mononuclear cell gene expression profiles identify emergent post-traumatic stress disorder among trauma survivors. Mol Psychiatry. 2005;10:500–13.
47. Tylee DS, Chandler SD, Nievergelt CM, Liu X, Pazol J, Woelk CH, et al. Blood-based gene-expression biomarkers of post-traumatic stress disorder among deployed marines: a pilot study. Psychoneuroendocrinology 2015;51:472–94.
48. Breen MS, Maihofer AX, Glatt SJ, Tylee DS, Chandler SD, Tsuang MT, et al. Gene networks specific for innate immunity define post-traumatic stress disorder. Mol Psychiatry. 2015;20:1538–45.
49. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 2010;26:2190–2191.
50. Newman AM, Liu CL, Green MR, Gentles AJ, Feng W, Xu Y, et al. Robust enumeration of cell subsets from tissue expression profiles. Nat Methods. 2015;12:453–457.
51. Duncan LE, Ratanatharathorn A, Aiello AE, Almli LM, Amstadter AB, Ashley-Koch AE, et al. Largest GWAS of PTSD (N=20 070) yields genetic overlap with schizophrenia and sex differences in heritability. Mol Psychiatry. 2018;23:666–73.
52. Garrett ME, Qin XJ, Mehta D, Dennis MF, Marx CE, Grant GA, et al. Gene expression analysis in three posttraumatic stress disorder cohorts implicates inflammation and innate immunity pathways and uncovers shared genetic risk with major depressive disorder. Front Neurosci. 2021;15:938.
53. Daskalakis NP, Rijal CM, King C, Huckins LM, Ressler KJ. Recent genetics and epigenetics approaches to PTSD. Curr Psychiatry Rep. 2018;20:30.
54. Neigh GN, Ali FF. Co-morbidity of PTSD and immune system dysfunction: opportunities for treatment. Curr Opin Pharm. 2016;29:104–10.
55. Wang Z, Caughron B, Young MRI. Posttraumatic stress disorder: an immunological disorder? Front Psychiatry. 2017;8:222.
56. Speer KE, Semple S, Naumovski N, D'Cunha NM, McKune AJ. HPA axis function and diurnal cortisol in post-traumatic stress disorder: a systematic review. Neurobiol Stress. 2019;11:100180.
57. Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, et al. Post-traumatic stress disorder. Nat Rev Dis Prim. 2015;1:1–22.
58. Nutt DJ, Malizia AL. Structural and functional brain changes in posttraumatic stress disorder. J Clin Psychiatry. 2004;65:11–17.
59. Li Z, Chen J, Yu H, He L, Xu Y, Zhang D, et al. Genome-wide association analysis identifies 30 new susceptibility loci for schizophrenia. Nat Genet. 2017;49:1576–83.
60. Jong S, de, Newhouse SJ, Patel H, Lee S, Dempster D, Curtis C, et al. Immune signatures and disorder-specific patterns in a cross-disorder gene expression analysis. Br J Psychiatry. 2016;209:202–208.
61. Tsolakidou A, Czibere L, Pütz B, Trümbach D, Panhuysen M, Deussing JM, et al. Gene expression profiling in the stress control brain region hypothalamic paraventricular nucleus reveals a novel gene network including Amyloid beta Precursor Protein. BMC Genomics. 2010;11:546.
62. Maccarrone G, Ditzen C, Yassouridis A, Rewerts C, Uhr M, Uhlen M, et al. Psychiatric patient stratification using biosignatures based on cerebrospinal fluid protein expression clusters. J Psychiatr Res. 2013;47:1572–80.
63. Hou Y, Liang W, Zhang J, Li Q, Ou H, Wang Z, et al. Schizophrenia-associated rs4702 G allele-specific downregulation of FURIN expression by miR-338-3p reduces BDNF production. Schizophr Res. 2018;199:176–80.
64. Schrode N, Ho S-M, Yamamuro K, Dobbyn A, Huckins L, Matos MR, et al. Synergistic effects of common schizophrenia risk variants. Nat Genet. 2019;51:1475–85.
65. English JA, Fan Y, Föcking M, Lopez LM, Hryniewiecka M, Wynne K, et al. Reduced protein synthesis in schizophrenia patient-derived olfactory cells. Transl Psychiatry. 2015;5:e663–e663.
66. Miron J, Picard C, Labonté A, Auld D, Breitner J, Poirier J. Association of PPP2R1A with Alzheimer's disease and specific cognitive domains. Neurobiol Aging. 2019;81:234–43.
67. Bralten J, Franke B, Waldman I, Rommelse N, Hartman C, Asherson P, et al. Candidate genetic pathways for Attention-Deficit/Hyperactivity Disorder (ADHD) show association to hyperactive/impulsive symptoms in children With ADHD. J Am Acad Child Adolesc Psychiatry. 2013;52:1204–1212.e1.
68. Chang W-S, Wang Y-H, Zhu X-T, Wu C-J. Genome-wide profiling of miRNA and mRNA expression in Alzheimer's disease. Med Sci Monit Int Med J Exp Clin Res. 2017;23:2721–31.
69. Kawai T, Morita K, Masuda K, Nishida K, Shikishima M, Ohta M, et al. Gene expression signature in peripheral blood cells from medical students exposed to chronic psychological stress. Biol Psychol. 2007;76:147–55.
70. Zhao Y, Liang X, Zhu F, Wen Y, Xu J, Yang J, et al. A large-scale integrative analysis of GWAS and common meQTLs across whole life course identifies genes, pathways and tissue/cell types for three major psychiatric disorders. Neurosci Biobehav Rev. 2018;95:347–52.
71. Konno T, Ross OA, Teive HAG, Sławek J, Dickson DW, Wszolek ZK. DCTN1-related neurodegeneration: Perry syndrome and beyond. Parkinsonism Relat Disord. 2017;41:14–24.
72. Seth A, Giunta S, Franceschil C, Kola I, Venanzoni MC. Regulation of the human stress response gene GADD153 expression: role of ETS1 and FLI-1 gene products. Cell Death Differ. 1999;6:902–907.
73. St-Louis É, Degrandmaison J, Grastilleur S, Génier S, Blais V, Lavoie C, et al. Involvement of the coatomer protein complex I in the intracellular traffic of the delta opioid receptor. Mol Cell Neurosci. 2017;79:53–63.
74. Bettayeb K, Hooli BV, Parrado AR, Randolph L, Varotsis D, Aryal S, et al. Relevance of the COPI complex for Alzheimer's disease progression in vivo. Proc Natl Acad Sci USA. 2016;113:5418–23.
75. Yang Y, Wang X, Ju W, Sun L, Zhang H. Genetic and expression analysis of COPI genes and Alzheimer's disease susceptibility. Front Genet. 2019;10:866.
76. Deng S, Liu J, Wu X, Lu W. Golgi apparatus: a potential therapeutic target for autophagy-associated neurological diseases. Front Cell Dev Biol. 2020;8:901.
77. Izumi K, Brett M, Nishi E, Drunat S, Tan E-S, Fujiki K, et al. ARCN1 mutations cause a recognizable craniofacial syndrome due to COPI-mediated transport defects. Am J Hum Genet. 2016;99:451–459.
78. Watkin LB, Jessen B, Wiszniewski W, Vece TJ, Jan M, Sha Y, et al. COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis. Nat Genet. 2015;47:654–60.

79. Jean F, Stuart A, Tarailo-Graovac M. Dissecting the genetic and etiological causes of primary microcephaly. Front Neurol. 2020;11:570830.
80. Sherin JE, Nemeroff CB. Post-traumatic stress disorder: the neurobiological impact of psychological trauma. Dialogues Clin Neurosci. 2011;13:263–78.
81. Giustino TF, Fitzgerald PJ, Maren S. Revisiting propranolol and PTSD: Memory erasure or extinction enhancement? Neurobiol Learn Mem. 2016;130:26–33.
82. Lippmann M, Cohen MD, Chen L-C. Health effects of World Trade Center (WTC) Dust: An unprecedented disaster with inadequate risk management. Crit Rev Toxicol. 2015;45:492–530.
83. Reibman J, Liu M, Cheng Q, Liautaud S, Rogers L, Lau S, et al. Characteristics of a Residential and Working Community With Diverse Exposure to World Trade Center Dust, Gas, and Fumes. J Occup Environ Med Am Coll Occup Environ Med. 2009;51:534–41.
84. Hervé M, Bergon A, Le Guisquet A-M, Leman S, Consoloni J-L, Fernandez-Nunez N, et al. Translational identification of transcriptional signatures of major depression and antidepressant response. Front Mol Neurosci. 2017;10:248.
85. Carlini V, Verduci I, Cianci F, Cannavale G, Fenoglio C, Galimberti D, et al. CLIC1 protein accumulates in circulating monocyte membrane during neurodegeneration. Int J Mol Sci. 2020;21:1484.
86. Tang T, Lang X, Xu C, Wang X, Gong T, Yang Y, et al. CLICs-dependent chloride efflux is an essential and proximal upstream event for NLRP3 inflammasome activation. Nat Commun. 2017;8:202.
87. Gurunathan G, Yu Z, Coulombe Y, Masson J-Y, Richard S. Arginine methylation of hnRNPUL1 regulates interaction with NBS1 and recruitment to sites of DNA damage. Sci Rep. 2015;5:10475.
88. Baker K, Qiao S-W, Kuo TT, Aveson VG, Platzer B, Andersen J-T, et al. Neonatal Fc receptor for IgG (FcRn) regulates cross-presentation of IgG immune complexes by CD8−CD11b+ dendritic cells. Proc Natl Acad Sci USA. 2011;108:9927–32.
89. Le-Niculescu H, Roseberry K, Levey DF, Rogers J, Kosary K, Prabha S, et al. Towards precision medicine for stress disorders: diagnostic biomarkers and targeted drugs. Mol Psychiatry. 2020;25:918–38.
90. Zhu X, Bührer C, Wellmann S. Cold-inducible proteins CIRP and RBM3, a unique couple with activities far beyond the cold. Cell Mol Life Sci. 2016;73:3839–59.
91. Zhou J-Y, Krovvidi RK, Gao Y, Gao H, Petritis BO, De A, et al. Trauma-associated human neutrophil alterations revealed by comparative proteomics profiling. Proteomics Clin Appl. 2013;7:571–83.
92. Lu Q, Shen N, Li XM, Chen SL. Genomic view of IFN-α response in pre-autoimmune NZB/W and MRL/lpr mice. Genes Immun. 2007;8:590–603.
93. Chen Y, Li X, Kobayashi I, Tsao D, Mellman TA. Expression and methylation in posttraumatic stress disorder and resilience; evidence of a role for odorant receptors. Psychiatry Res. 2016;245:36–44.
94. Breen MS, Bierer LM, Daskalakis NP, Bader HN, Makotkine I, Chattopadhyay M, et al. Differential transcriptional response following glucocorticoid activation in cultured blood immune cells: a novel approach to PTSD biomarker development. Transl Psychiatry. 2019;9:201.
95. Glover DA, Steele AC, Stuber ML, Fahey JL. Preliminary evidence for lymphocyte distribution differences at rest and after acute psychological stress in PTSD-symptomatic women. Brain Behav Immun. 2005;19:243–51.
96. Lemieux A, Coe CL, Carnes M. Symptom severity predicts degree of T cell activation in adult women following childhood maltreatment. Brain Behav Immun. 2008;22:994–1003.
97. Skapenko A, Leipe J, Lipsky PE, Schulze-Koops H. The role of the T cell in autoimmune inflammation. Arthritis Res Ther. 2005;7:S4–S14.
98. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol Psychiatry. 2016;21:642–649.
99. Dong Y, Li S, Lu Y, Li X, Liao Y, Peng Z, et al. Stress-induced NLRP3 inflammasome activation negatively regulates fear memory in mice. J Neuroinflammation. 2020;17:205.
100. Fonkoue IT, Marvar PJ, Norrholm S, Li Y, Kankam ML, Jones TN, et al. Symptom severity impacts sympathetic dysregulation and inflammation in post-traumatic stress disorder (PTSD). Brain Behav Immun. 2020;83:260–269.
101. Michopoulos V, Powers A, Gillespie CF, Ressler KJ, Jovanovic T. Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. Neuropsychopharmacology. 2017;42:254–70.
102. Speer K, Upton D, Semple S, McKune A. Systemic low-grade inflammation in post-traumatic stress disorder: a systematic review. J Inflamm Res. 2018;11:111–21.

AUTHOR CONTRIBUTIONS

AF, RHP, SMS, RY, NPD, KK, LMB, SM, and LMH designed the present study and provided conceptual input. MC, JMM, IGU, and DJH led collection of data during participants' first health-monitoring visit to the WTC Health Program, which were incorporated into analyses for the present study. AF, RHP, LC, OD, LC, CA, JS, SRH, RY, FD, IM, LMB, CS, JSJ, and JDF conducted the study. SM, LMH, RHP, and PR conducted the data analyses. SM, LMH, AF, and RHP wrote the paper. RY, SMS, CS, CA and DSC provided input on the manuscript draft. This study was funded by CDC/NIOSH U01 OH010986 (MPIs AF and RHP) and CDC/NIOSH U01 OH010407 (MPIs AF, RHP, and SMS).

COMPETING INTERESTS

AF and DSC are named co-inventors on a patent application in the US, and several issued patents outside the US, filed by the Icahn School of Medicine at Mount Sinai (ISMMS) related to the use of ketamine for the treatment of PTSD. This intellectual property has not been licensed. DSC is named co-inventor on patents filed by the ISMMS relating to the treatment for treatment-resistant depression, suicidal ideation and other disorders. ISMMS has entered into a licensing agreement with Janssen Pharmaceuticals, Inc. and it has and will receive payments from Janssen under the license agreement related to these patents for the treatment of treatment-resistant depression and suicidal ideation. Consistent with the ISMMS Faculty Handbook (the medical school policy), DSC is entitled to a portion of the payments received by the ISMMS. Since SPRAVATO has received regulatory approval for treatment-resistant depression, ISMMS and thus, through the ISMMS, DSC will be entitled to additional payments, beyond those already received, under the license agreement. DSC is a named co-inventor on several patents filed by ISMMS for a cognitive training intervention to treat depression and related psychiatric disorders. The ISMMS has entered into a licensing agreement with Click Therapeutics, Inc. and has and will receive payments related to the use of this cognitive training intervention for the treatment of psychiatric disorders. In accordance with the ISMMS Faculty Handbook, DSC has received a portion of these payments and is entitled to a portion of any additional payments that the medical school might receive from this license with Click Therapeutics. DSC is a named co-inventor on a patent application filed by the ISMMS for the use of intranasally administered Neuropeptide Y (NPY) for the treatment of mood and anxiety disorders. This intellectual property has not been licensed. The other authors declare no conflicts of interest.

ADDITIONAL INFORMATION

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