nature genetics

Article

https://doi.org/10.1038/s41588-024-01707-9

Genome-wide association analyses identify 95 risk loci and provide insights into the neurobiology of post-traumatic stress disorder

Received: 24 May 2023

Accepted: 5 March 2024

Published online: 18 April 2024

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Post-traumatic stress disorder (PTSD) genetics are characterized by lower discoverability than most other psychiatric disorders. The contribution to biological understanding from previous genetic studies has thus been limited. We performed a multi-ancestry meta-analysis of genome-wide association studies across 1,222,882 individuals of European ancestry (137,136 cases) and 58,051 admixed individuals with African and Native American ancestry (13,624 cases). We identified 95 genome-wide significant loci (80 new). Convergent multi-omic approaches identified 43 potential causal genes, broadly classified as neurotransmitter and ion channel synaptic modulators (for example, *GRIA1*, *GRM8* and *CACNA1E*), developmental, axon guidance and transcription factors (for example, *FOXP2*, *EFNA5* and *DCC*), synaptic structure and function genes (for example, *PCLO*, *NCAM1* and *PDE4B*) and endocrine or immune regulators (for example, *ESR1*, *TRAF3* and *TANK*). Additional top genes influence stress, immune, fear and threat-related processes, previously hypothesized to underlie PTSD neurobiology. These findings strengthen our understanding of neurobiological systems relevant to PTSD pathophysiology, while also opening new areas for investigation.

Post-traumatic stress disorder (PTSD) is characterized by intrusive thoughts, hyperarousal, avoidance and negative alterations in cognition and mood that can become persistent for some individuals after traumatic event exposure. Approximately 5.6% of trauma-exposed adults worldwide have PTSD during their lifetimes, and rates are higher in those with high levels and certain types of trauma exposure such as combat survivors and assault victims[1]. PTSD is a chronic condition for many, posing a substantial quality-of-life and economic burden to individuals and society[2].

Substantial advances are being made in the understanding of PTSD biology through preclinical studies[3], many of which are focused on fear systems in the brain, and some of which are being translated to human studies of PTSD[4]. Human neuroimaging studies highlight probable dysfunction in brain fear circuitry that includes deficits in top–down modulation of the amygdala by regulatory regions such as the anterior cingulate and ventromedial prefrontal cortex[5,6]. Neuroendocrine studies have identified abnormalities in the hypothalamic–pituitary–adrenal axis and glucocorticoid-induced gene expression in the development and maintenance of PTSD[7,8]. However, many questions remain about the pathophysiology of PTSD, and new targets are needed for prevention and treatment.

While twin and genetic studies demonstrated that the risk of developing PTSD conditional on trauma exposure is partly driven by genetic factors[9,10], the specific characterization of the genetic

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https://doi.org/10.1038/s41588-024-01707-9

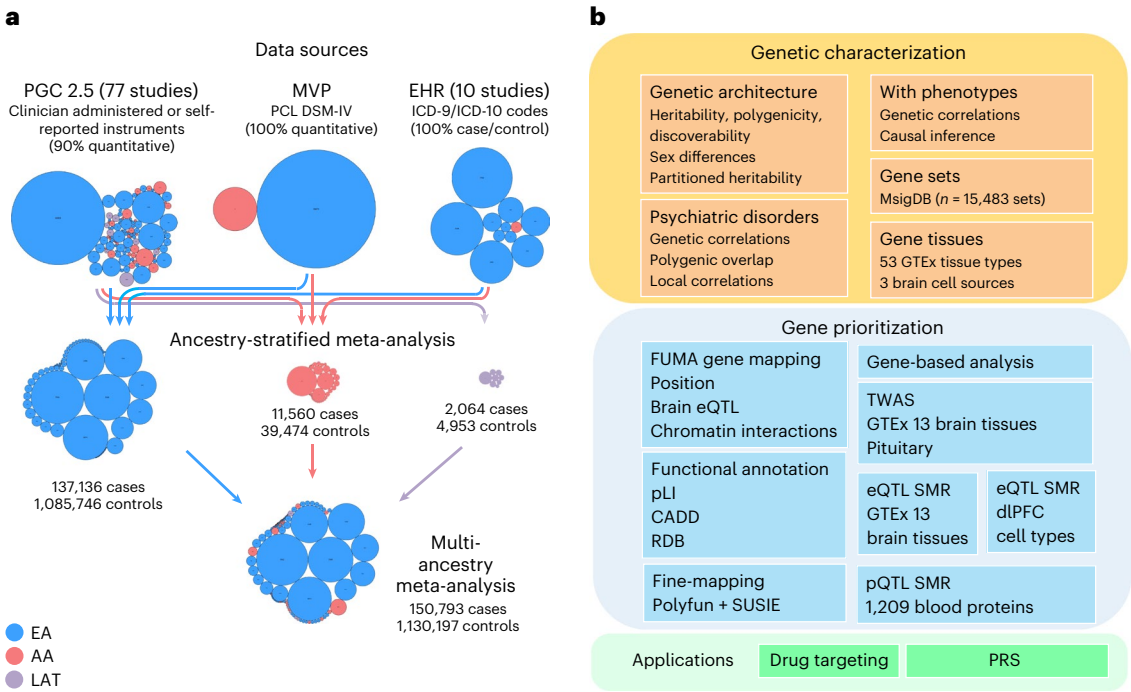

Fig. 1 | Data sources and analyses in PTSD Freeze 3. a, Data sources of GWAS included in PGC-PTSD Freeze 3. Collections of contributing studies are pictured as bubble plots where each circle represents a contributing study. Circle areas are proportional to sample size and colors indicate the ancestry classification of participants (blue, EA; red, AA and purple, LAT). Arrowed lines indicate data sources being pooled together to perform GWAS meta-analyses stratified by ancestry. **b**, Methods applied for genetic characterization of PTSD, gene prioritization analyses and translational applications.

architecture of PTSD is just emerging as very large meta-analyses of genome-wide association studies (GWAS) become available. Recent research by our workgroup—the Psychiatric Genomic Consortium for PTSD (PGC-PTSD)[11,12] and the VA Million Veteran Program (MVP)[13]—contributed to an increased appreciation for the genetic complexity of PTSD as a highly polygenic disorder. Despite sample sizes of over 200,000 individuals, these studies identified at most 16 PTSD risk loci, which were not consistent across datasets, indicating the necessity of still larger sample sizes. In addition, these studies did not examine the X chromosome, which comprises 5% of the human genome, and may be particularly important given sex differences in PTSD prevalence.

Furthermore, GWAS to date have had limited power to identify credible treatment candidates. PTSD is also known frequently to be comorbid and genetically correlated with other mental (for example, major depressive disorder (MDD) and attention deficit hyperactivity disorder)[14] and physical health conditions (for example, cardiovascular disease and obesity)[15–17], but studies to date are limited in their ability to parse shared and disorder-specific loci and link them to underlying biological systems. Importantly, previous GWAS are severely limited in generalizing their findings to non-European ancestries. Recent work on polygenic risk scores (PRS) in PTSD shows the potential utility of these measures in research[16–18], but also, vexingly, limited cross-population transferability. Without expansion to other ancestries, there is a risk that recent advances in PTSD genetics will result in the widening of research and treatment disparities. This inequity is particularly troubling in the US given the disproportionately high burden of trauma and PTSD faced by populations of African, Native and Latin American origin[19,20].

In the present analysis, we synthesize data from 88 studies to perform a multi-ancestry meta-analysis of GWAS data from European ancestry (EA; $n = 137{,}136$ cases and $n = 1{,}085{,}746$ controls), African ancestry (AA; $n = 11{,}560$ cases and $n = 39{,}474$ controls) and Native American ancestry (including individuals from Latin America (LAT); $n = 2{,}064$ cases and $n = 4{,}953$ controls) samples, including analyses of the X chromosome. We follow up on GWAS findings to examine global and local heritability, infer the involvement of brain regions and neuronal systems using transcriptomic data, describe shared genetic effects with comorbid conditions and use multi-omic data to prioritize a set of 43 putatively causal genes (Fig. 1). Finally, we use this information to identify potential candidate pathways for future PTSD treatment studies. Together, these findings mark significant progress toward discovering the pathophysiology of trauma- and stress-related disorders and inform future intervention approaches for PTSD and related conditions.

Results

Data collection and GWAS

The PGC-PTSD[21] Freeze 3 data collection includes 1,307,247 individuals from 88 studies (Supplementary Table 1). Data in this freeze were assembled from the following three primary sources (Fig. 1a): PTSD studies based on clinician-administered or self-reported instruments (Freeze 2.5 (refs. 11,12) plus subsequently collected studies), MVP release 3 GWAS using the Post-traumatic Stress Disorder Checklist (PCL for DSM-IV)[13] and ten biobank studies with electronic health record (EHR)-derived PTSD status. We included 95 GWAS, including EA ($n = 1{,}222{,}882$; effective sample size (n_{eff}) = 641,533), AA ($n = 51{,}034$; $n_{eff} = 42{,}804$) and LAT ($n = 7{,}017$; $n_{eff} = 6{,}530$) participants (Supplementary Table 2).

EA PTSD GWAS

Population, screening and case ascertainment differences between datasets led to the assumption that there would be substantial cross-dataset variation in PTSD genetic signal. We investigated this possibility using the software MiXeR[22,23]. Overall, we found no evidence for subset-specific genetic causal variation (see Supplementary Note, Supplementary Tables 3 and 4 and Extended Data Fig. 1 for further details). Given the similarities of the PTSD subsets, we performed a sample-size weighted fixed-effects meta-analysis of GWAS. For the EA meta-analysis

https://doi.org/10.1038/s41588-024-01707-9

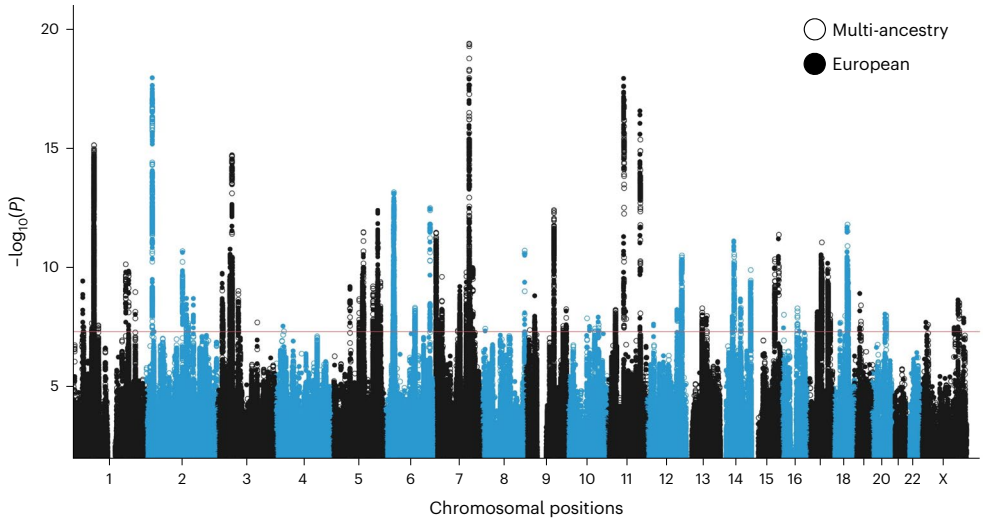

Fig. 2 | GWAS meta-analyses in European and multi-ancestry individuals identify a total of 95 PTSD risk loci. Overlaid Manhattan plots of EA (n = 137,136 cases and n = 1,085,746 controls) and multi-ancestry meta-analyses (n = 150,760 cases and n = 1,130,173 controls), showing 81 GWS loci for the EA (full circles) and 85 GWS loci for the multi-ancestry (hollow circles) analyses. Circle colors alternate between chromosomes, with even chromosomes colored blue and odd chromosomes colored black. The y axis refers to $-\log_{10}(P)$ from two-sided z tests for meta-analysis effect estimates. The horizontal red bar indicates the threshold for GWS associations ($P < 5 \times 10^{-8}$).

(n = 137,136 cases and n = 1,085,746 controls), the genomic control (GC)-λ was 1.55, the linkage disequilibrium score regression (LDSC)[24] intercept was 1.0524 (s.e. = 0.0097; Supplementary Table 5) and the attenuation ratio was 0.0729 (s.e. = 0.0134), indicating that 92.7% of the observed inflation in test statistics was due to polygenic signal; thus, artifacts produced only minimal inflation.

The EA meta-analysis identified 81 independent genome-wide significant (GWS) loci, including 5 GWS loci on the X chromosome (Extended Data Fig. 2, Supplementary Figs. 1 and 2, Supplementary Table 6, regional association plots in Supplementary Data 1, forest plots in Supplementary Data 2 and Supplementary Note). Relative to recent previous PTSD GWAS, 67 loci are new[11–13] (Supplementary Table 7). No region exhibited significant effect size heterogeneity (Supplementary Fig. 3).

We next sought to gain insights into whether loci harbor multiple independent variants. While FUMA[25] annotations reported independent lead SNPs within risk loci based on pair-wise linkage disequilibrium (LD; Supplementary Table 8), COJO[26] analysis of each locus conditional on the leading variants suggested that only one locus carried a conditionally independent GWS SNP (rs3132388 on chromosome 6, $P = 2.86 \times 10^{-9}$). This locus, however, is in the major histocompatibility complex (MHC) region, whose complicated LD structure[27] may not be accurately captured by reference panels.

AA and LAT PTSD GWAS meta-analyses

The AA meta-analysis included 51,034 predominantly admixed individuals (n = 11,560 cases and n = 39,474 controls). There was minimal inflation of test statistics, with GC-λ = 1.031. No GWS loci were identified (Supplementary Fig. 4). The LAT meta-analysis was performed in 7,017 individuals (n = 2,064 cases and n = 4,953 controls). There was minimal inflation of test statistics (GC-λ = 0.993), and no GWS loci were identified (Supplementary Fig. 5).

Multi-ancestry GWAS meta-analysis

A multi-ancestry fixed-effects meta-analysis of EA, AA and LAT GWAS (n = 150,793 cases and n = 1,130,197 controls) identified 85 GWS loci. Compared to the EA meta-analysis, 10 loci lost GWS, while 14 previously suggestive loci ($P < 5 \times 10^{-7}$) became GWS (Fig. 2). In total, the present study identified 95 unique GWS PTSD loci between the EA and multi-ancestry meta-analyses (Table 1). Due to the complex local ancestry structure in AA and LAT individuals, which complicates LD modeling, we focused subsequent fine-mapping analyses (Fig. 1b) on data from the EA GWAS.

Gene mapping

To link GWS SNPs to relevant protein-coding genes, we applied the following three gene-mapping approaches implemented in FUMA: positional mapping, expression quantitative trait loci (eQTL) and chromatin interaction mapping (Supplementary Table 9). GWS SNPs within the 81 EA loci mapped to 415 protein-coding genes under at least one mapping strategy. A total of 230 (55%) genes were mapped by two or more strategies, and 85 (20%) genes were mapped by all three strategies (Supplementary Fig. 6). Notably, some genes were implicated across independent risk loci by chromatin interactions/eQTL mapping, including *EFNA5*, *GRIA1*, *FOXP2*, *MDFIC*, *WSB2*, *VSIG10*, *PEBP1* and *C17orf58*. Chromatin interaction plots are shown in Supplementary Data 3.

Functional annotation and fine-mapping of risk loci

Functional annotations were used to gain insights into the functional role of SNPs within the 81 risk loci (Supplementary Table 10)—72 loci contained at least one SNP with combined annotation-dependent depletion (CADD)[28] scores suggestive of deleteriousness to gene function (≥12.37), 43 loci contained GWS SNPs with RegulomeDB (RDB)[29] scores likely to affect binding and 23 loci contained at least one SNP in the exon region of a gene.

To narrow the credible window of risk loci and identify potentially causal SNPs, we fine-mapped loci using PolyFun+SUSIE[30], which identified a credible set for 67 loci. Credible set window lengths were on average 62% of the original set lengths (Supplementary Table 11) and contained a median of 23 credible SNPs (range 1–252). Only one contained an SNP with posterior inclusion probability >0.95, a missense SNP in the exon of *ANAPC4* (rs34811474, R(CGA)>Q(CAA); Supplementary Table 12).

Gene-based, gene-set and gene-tissue analyses

As an alternative approach to SNP-based association analysis, we tested the joint association of markers within genes using a gene-based association analysis in MAGMA[31], which is a two-stage method that first maps SNPs to genes and then tests whether a gene is significantly associated with PTSD. The gene-based analysis identified 175 GWS genes

https://doi.org/10.1038/s41588-024-01707-9

Table 1 | GWS loci associated with PTSD in the multi-ancestry and European PGC-PTSD Freeze 3 data

Locus[a]	Lead SNP[b]	Chr	Start	Stop	A1	A2	Multi-ancestry[c](150,793 cases,1,130,197 controls)			EA[c](137,136 cases,1,085,746 controls)			AA[c](11,560 cases,39,474 controls)			LAT[c](2,064 cases,4,953 controls)		
							A1 Freq	Z score	P value[d]	A1 Freq	Z score	P value[d]	A1 Freq	Z score	P value[d]	A1 Freq	Z score	P value[d]
1	rs78201023	1	35,664,657	36,375,226	T	C	NA	NA	NA	0.038	6.264	**3.76×10^{-10}**	NA	NA	NA	NA	NA	NA
2	rs617099	1	38,198,744	38,459,210	A	T	0.692	−5.525	**3.30×10^{-8}**	0.713	−5.283	1.27×10^{-7}	0.386	−1.859	0.06	0.585	0.283	0.78
2	rs12026766	1	38,198,744	38,459,210	A	G	0.277	5.425	5.80×10^{-8}	0.272	5.538	**3.06×10^{-8}**	0.329	0.358	0.72	0.399	−0.028	0.98
3	rs2186120	1	66,392,405	66,584,457	A	G	0.504	5.592	**2.24×10^{-8}**	0.529	5.388	7.12×10^{-8}	0.146	2.314	0.02	0.422	−1.787	0.07
3	rs7519259	1	66,392,405	66,547,212	A	G	0.511	5.335	9.58×10^{-8}	0.532	5.514	**3.50×10^{-8}**	0.198	0.665	0.51	0.426	−1.500	0.13
4	rs10789373	1	73,279,823	74,108,971	C	G	0.606	−8.061	**7.59×10^{-16}**	0.619	−7.828	**4.95×10^{-15}**	0.447	−2.193	0.03	0.320	0.290	0.77
4	rs12128161	1	73,275,828	74,099,273	A	C	0.608	−7.946	**1.93×10^{-15}**	0.615	−7.882	**3.23×10^{-15}**	0.539	−1.640	0.10	0.328	0.587	0.56
5	rs2207285	1	88,790,511	88,836,922	A	C	0.157	−5.557	**2.75×10^{-8}**	0.158	−5.311	1.09×10^{-7}	0.157	−1.132	0.26	0.144	−1.610	0.11
6	rs169235	1	181,698,693	181,747,349	A	G	0.747	−6.509	**7.56×10^{-11}**	0.751	−6.191	**6.00×10^{-10}**	0.702	−1.560	0.12	0.651	−1.598	0.11
6	rs4652676	1	181,698,693	181,747,349	A	G	0.251	6.247	**4.19×10^{-10}**	0.248	6.396	**1.60×10^{-10}**	0.280	−0.284	0.78	0.349	1.553	0.12
7	rs9287117	1	191,154,894	191,418,368	T	C	0.384	6.378	**1.80×10^{-10}**	0.369	6.390	**1.66×10^{-10}**	0.630	0.736	0.46	0.256	0.439	0.66
7	rs9651063	1	191,154,894	191,418,368	T	C	0.378	6.337	**2.35×10^{-10}**	0.367	6.409	**1.47×10^{-10}**	0.553	0.602	0.55	0.253	0.181	0.86
8	rs2011374	1	214,094,735	214,139,159	A	T	0.510	−6.093	**1.11×10^{-9}**	0.505	−5.738	**9.58×10^{-9}**	0.600	−0.760	0.45	0.389	−3.818	0.00
9	rs10865093	2	22,430,795	22,613,427	T	C	0.545	−8.585	**9.08×10^{-18}**	0.541	−8.736	**2.41×10^{-18}**	0.645	−0.548	0.58	0.255	−0.279	0.78
9	rs6759922	2	22,430,795	22,613,427	A	G	0.460	8.572	**1.01×10^{-17}**	0.457	8.821	**1.13×10^{-18}**	0.461	0.163	0.87	0.746	0.299	0.76
10	rs1866560	2	27,186,507	27,345,484	T	G	0.464	−5.448	5.11×10^{-8}	0.449	−5.455	**4.89×10^{-8}**	0.658	−1.253	0.21	0.661	1.210	0.23
11	rs10496632	2	124,953,763	125,053,393	C	G	0.282	−6.698	**2.12×10^{-11}**	0.286	−6.680	**2.40×10^{-11}**	0.206	−0.839	0.40	0.330	−0.528	0.60
12	rs6430728	2	138,097,204	138,334,702	A	G	0.526	5.683	**1.33×10^{-8}**	0.511	5.996	**2.02×10^{-9}**	0.747	−0.008	0.99	0.548	−0.959	0.34
13	rs28380327	2	144,145,478	144,263,280	A	T	0.657	5.593	**2.23×10^{-8}**	0.642	5.355	8.58×10^{-8}	0.864	1.711	0.09	0.811	0.085	0.93
13	rs10191758	2	144,145,478	144,272,229	A	G	0.637	5.517	**3.44×10^{-8}**	0.626	5.487	**4.08×10^{-8}**	0.789	0.860	0.39	0.803	0.150	0.88
14	rs197261	2	161,866,881	162,095,003	A	G	0.727	5.373	7.74×10^{-8}	0.718	5.994	**2.05×10^{-9}**	0.837	−1.129	0.26	0.851	−1.276	0.20
15	rs6800583	3	16,843,737	16,879,208	A	G	0.383	6.117	**9.54×10^{-10}**	0.373	6.366	**1.95×10^{-10}**	0.541	0.157	0.88	0.360	−0.578	0.56
15	rs748832	3	16,843,737	16,879,208	A	G	0.618	−5.785	**7.25×10^{-9}**	0.627	−6.377	**1.80×10^{-10}**	0.483	1.219	0.22	0.641	0.583	0.56
16	rs4373086	3	18,611,283	18,824,298	A	G	0.732	5.648	**1.62×10^{-8}**	0.722	5.765	**8.19×10^{-9}**	0.878	1.166	0.24	0.758	−2.025	0.04
16	rs6800637	3	18,611,283	18,824,298	A	T	0.722	5.599	**2.15×10^{-8}**	0.711	5.923	**3.16×10^{-9}**	0.853	0.520	0.60	0.747	−2.028	0.04
17	rs6801151	3	43,249,957	43,591,405	A	G	0.163	6.326	**2.52×10^{-10}**	0.156	6.098	**1.08×10^{-9}**	0.275	1.860	0.06	0.065	−0.132	0.90
17	rs6802567	3	43,249,957	43,594,564	T	C	0.876	−6.263	**3.79×10^{-10}**	0.883	−6.726	**1.74×10^{-11}**	0.763	0.959	0.34	0.953	−0.155	0.88
18	rs7431106	3	49,734,229	50,644,134	A	G	0.491	7.941	**2.00×10^{-15}**	0.488	7.304	**2.78×10^{-13}**	0.582	3.090	0.00	0.247	1.372	0.17
18	rs11130221	3	49,734,229	50,644,134	C	G	0.511	−7.792	**6.60×10^{-15}**	0.513	−7.328	**2.33×10^{-13}**	0.450	−2.410	0.02	0.752	−1.337	0.18
19	rs1541903	3	71,303,875	71,344,078	T	C	0.129	6.111	**9.91×10^{-10}**	0.134	5.939	**2.87×10^{-9}**	0.077	1.228	0.22	0.044	0.842	0.40
20	rs28758576	3	135,476,532	135,602,459	T	C	0.898	−5.606	**2.08×10^{-8}**	0.892	−5.305	1.13×10^{-7}	0.978	−1.675	0.09	0.968	−0.806	0.42
21	rs34811474	4	25,342,606	25,408,838	A	G	0.211	−5.395	6.85×10^{-8}	0.223	−5.544	**2.95×10^{-8}**	0.054	−0.454	0.65	0.076	0.640	0.52
22	rs12509393	4	28,273,059	28,347,050	T	C	0.255	−5.456	**4.87×10^{-8}**	0.262	−5.188	2.13×10^{-7}	0.136	−1.597	0.11	0.325	−0.619	0.54
23	rs10939933	5	61,398,053	61,683,591	C	G	0.509	5.956	**2.58×10^{-9}**	0.517	6.161	**7.23×10^{-10}**	0.387	0.358	0.72	0.472	−0.736	0.46

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Table 1 (continued) | GWS loci associated with PTSD in the multi-ancestry and European PGC-PTSD Freeze 3 data

Locus[a]	Lead SNP[b]	Chr	Start	Stop	A1	A2	Multi-ancestry[c](150,793 cases,1,130,197 controls)			EA[c](137,136 cases,1,085,746 controls)			AA[c](11,560 cases,39,474 controls)			LAT[c](2,064 cases,4,953 controls)		
							A1 Freq	*Z* score	*P* value[d]	A1 Freq	*Z* score	*P* value[d]	A1 Freq	*Z* score	*P* value[d]	A1 Freq	*Z* score	*P* value[d]
23	rs12521971	5	61,398,053	61,683,591	A	C	0.509	5.942	**2.81×10^{-9}**	0.517	6.178	**6.49×10^{-10}**	0.386	0.237	0.81	0.472	−0.739	0.46
24	rs4489042	5	92,362,700	92,538,853	C	G	0.401	−5.983	**2.19×10^{-9}**	0.382	−5.610	**2.02×10^{-8}**	0.662	−2.045	0.04	0.554	−0.700	0.48
25	rs6867409	5	103,684,787	104,055,261	T	C	0.465	5.961	**2.50×10^{-9}**	0.461	5.973	**2.33×10^{-9}**	0.506	0.688	0.49	0.597	0.352	0.73
25	rs33817	5	103,791,044	104,055,261	A	G	0.421	5.942	**2.82×10^{-9}**	0.428	6.358	**2.04×10^{-10}**	0.314	−0.440	0.66	0.451	−0.814	0.42
26	rs295017	5	106,118,410	106,215,439	A	G	0.298	5.808	**6.31×10^{-9}**	0.309	5.597	**2.19×10^{-8}**	0.159	1.265	0.21	0.139	1.034	0.30
27	rs13161115	5	106,918,329	107,084,359	C	G	0.226	−6.961	**3.38×10^{-12}**	0.238	−6.615	**3.72×10^{-11}**	0.060	−2.664	0.01	0.078	0.767	0.44
27	rs13161130	5	106,918,329	107,060,400	C	G	0.232	−6.955	**3.54×10^{-12}**	0.242	−6.650	**2.94×10^{-11}**	0.094	−2.508	0.01	0.081	0.785	0.43
28	rs34425	5	107,349,092	107,769,562	A	T	0.317	6.172	**6.75×10^{-10}**	0.307	6.130	**8.80×10^{-10}**	0.475	1.230	0.22	0.170	−0.313	0.75
29	rs175086	5	139,517,197	139,700,608	A	G	0.514	6.182	**6.35×10^{-10}**	0.517	5.817	**5.99×10^{-9}**	0.498	1.860	0.06	0.356	1.142	0.25
30	rs251352	5	140,225,137	140,331,337	A	G	0.540	−5.581	**2.39×10^{-8}**	0.555	−5.203	1.96×10^{-7}	0.354	−1.476	0.14	0.478	−1.961	0.05
31	rs4257818	5	152,505,453	152,610,561	A	C	0.388	5.944	**2.79×10^{-9}**	0.405	5.942	**2.82×10^{-9}**	0.198	0.628	0.53	0.164	0.741	0.46
32	rs11167640	5	153,085,668	153,241,171	T	C	0.776	5.824	**5.75×10^{-9}**	0.778	5.869	**4.39×10^{-9}**	0.791	0.617	0.54	0.463	0.138	0.89
32	rs13168358	5	153,085,668	153,255,743	T	C	0.224	−5.823	**5.79×10^{-9}**	0.222	−5.873	**4.27×10^{-9}**	0.209	−0.594	0.55	0.537	−0.138	0.89
33	rs2135029	5	155,730,681	155,912,474	A	G	0.615	−6.812	**9.64×10^{-12}**	0.606	−7.251	**4.14×10^{-13}**	0.774	0.790	0.43	0.435	−0.226	0.82
34	rs11957630	5	164,467,717	164,678,946	A	G	0.446	−6.249	**4.14×10^{-10}**	0.458	−5.847	**5.01×10^{-9}**	0.298	−2.021	0.04	0.250	−1.147	0.25
35	rs28986300	6	26,748,873	29,607,101	A	G	0.936	−7.468	**8.14×10^{-14}**	0.939	−7.343	**2.09×10^{-13}**	0.908	−1.056	0.29	0.851	−1.334	0.18
35	rs29242	6	25,846,381	29,607,101	T	C	0.947	−7.368	**1.73×10^{-13}**	0.946	−7.464	**8.39×10^{-14}**	0.979	−0.272	0.79	0.865	−1.117	0.26
36	rs180963	6	100,914,602	101,339,400	T	C	0.493	5.848	**4.99×10^{-9}**	0.496	5.468	**4.56×10^{-8}**	0.465	2.030	0.04	0.383	0.756	0.45
37	rs9479138	6	152,201,201	152,264,529	T	G	0.372	7.282	**3.30×10^{-13}**	0.349	7.272	**3.54×10^{-13}**	0.670	1.377	0.17	0.599	−0.668	0.50
38	rs868754	7	1,833,097	2,110,850	C	G	0.195	−6.954	**3.54×10^{-12}**	0.205	−6.791	**1.11×10^{-11}**	0.067	−1.506	0.13	0.098	−0.363	0.72
38	rs34809719	7	1,809,618	2,110,850	T	G	0.199	−6.943	**3.85×10^{-12}**	0.209	−6.849	**7.43×10^{-12}**	0.067	−1.228	0.22	0.098	−0.372	0.71
39	rs10264275	7	3,521,658	3,715,667	A	G	0.763	5.663	**1.49×10^{-8}**	0.762	5.287	1.24×10^{-7}	0.796	2.115	0.03	0.618	0.446	0.66
39	rs35791987	7	3,521,658	3,715,667	C	G	0.239	−5.653	**1.58×10^{-8}**	0.237	−5.519	**3.40×10^{-8}**	0.247	−1.078	0.28	0.380	−0.670	0.50
40	rs13237518	7	12,233,848	12,285,140	A	C	0.435	5.006	5.55×10^{-7}	0.414	5.457	**4.83×10^{-8}**	0.689	−0.699	0.48	0.627	−0.445	0.66
41	rs4722031	7	21,468,640	21,555,536	A	T	0.294	6.325	**2.53×10^{-10}**	0.308	5.798	**6.69×10^{-9}**	0.117	3.441	0.00	0.228	−1.389	0.16
41	rs2107448	7	21,468,640	21,555,536	T	C	0.572	−5.958	**2.55×10^{-9}**	0.581	−5.823	**5.78×10^{-9}**	0.492	−1.725	0.08	0.273	0.846	0.40
42	rs4732514	7	75,607,155	75,852,480	T	C	0.645	5.470	**4.51×10^{-8}**	0.660	5.026	5.00×10^{-7}	0.425	2.385	0.02	0.575	0.347	0.73
43	rs58043442	7	82,386,297	82,641,937	T	C	0.474	−5.753	**8.79×10^{-9}**	0.488	−6.179	**6.44×10^{-10}**	0.278	0.370	0.71	0.394	1.116	0.26
44	rs2470937	7	104,558,434	105,063,372	A	T	0.454	6.391	**1.65×10^{-10}**	0.450	6.246	**4.22×10^{-10}**	0.506	1.469	0.14	0.493	0.069	0.95
45	rs1476535	7	113,858,363	114,290,415	T	C	0.576	9.183	**4.18×10^{-20}**	0.561	8.807	**1.28×10^{-18}**	0.765	2.564	0.01	0.605	0.589	0.56
46	rs7806900	7	114,940,147	115,113,279	A	G	0.535	6.258	**3.91×10^{-10}**	0.519	5.981	**2.22×10^{-9}**	0.769	1.786	0.07	0.531	0.507	0.61
47	rs2214230	7	117,502,574	117,668,235	T	G	0.374	6.166	**7.01×10^{-10}**	0.385	5.885	**3.98×10^{-9}**	0.229	1.257	0.21	0.228	1.859	0.06
47	rs61702433	7	117,502,574	117,636,111	T	G	0.348	6.053	**1.42×10^{-9}**	0.362	5.994	**2.05×10^{-9}**	0.160	0.507	0.61	0.220	1.568	0.12
48	rs34618371	7	124,392,512	124,710,858	T	C	0.607	−5.500	**3.80×10^{-8}**	0.602	−5.054	4.33×10^{-7}	0.703	−1.551	0.12	0.553	−2.510	0.01

https://doi.org/10.1038/s41588-024-01707-9

Table 1 (continued) | GWS loci associated with PTSD in the multi-ancestry and European PGC-PTSD Freeze 3 data

Locus[a]	Lead SNP[b]	Chr	Start	Stop	A1	A2	Multi-ancestry[c](150,793 cases,1,130,197 controls)			EA[c](137,136 cases,1,085,746 controls)			AA[c](11,560 cases,39,474 controls)			LAT[c](2,064 cases,4,953 controls)		
							A1 Freq	Z score	P value[d]	A1 Freq	Z score	P value[d]	A1 Freq	Z score	P value[d]	A1 Freq	Z score	P value[d]
49	rs10487459	7	126,371,011	126,507,903	A	G	0.622	−6.441	**1.19×10^{-10}**	0.612	−6.460	**1.05×10^{-10}**	0.768	−1.219	0.22	0.638	0.912	0.36
50	rs10104247	8	9,397,184	9,641,034	A	C	0.814	−5.501	**3.77×10^{-8}**	0.816	−5.462	**4.71×10^{-8}**	0.762	−1.258	0.21	0.906	0.681	0.50
51	rs4129585	8	143,297,329	143,479,815	A	C	0.412	6.705	**2.02×10^{-11}**	0.432	6.654	**2.85×10^{-11}**	0.135	1.346	0.18	0.209	−0.438	0.66
52	rs13284172	9	14,578,127	14,688,114	T	C	0.628	−5.478	**4.29×10^{-8}**	0.626	−5.211	1.88×10^{-7}	0.642	−1.846	0.06	0.783	0.023	0.98
53	rs13290462	9	31,124,452	31,251,063	T	G	0.679	5.610	**2.02×10^{-8}**	0.669	6.037	**1.58×10^{-9}**	0.791	−1.095	0.27	0.709	1.196	0.23
54	rs10821163	9	96,106,521	96,386,972	C	G	0.339	−7.255	**4.00×10^{-13}**	0.355	−6.915	**4.67×10^{-12}**	0.102	−1.956	0.05	0.313	−1.067	0.29
54	rs10992779	9	96,181,075	96,381,916	A	G	0.661	7.131	**9.96×10^{-13}**	0.647	6.982	**2.92×10^{-12}**	0.874	1.239	0.22	0.688	0.970	0.33
55	rs4838242	9	127,765,978	127,898,032	A	G	0.470	5.546	**2.92×10^{-8}**	0.472	5.080	3.78×10^{-7}	0.410	1.805	0.07	0.674	2.080	0.04
56	rs515805	9	137,932,302	137,965,157	A	G	0.185	5.824	**5.75×10^{-9}**	0.187	5.567	**2.60×10^{-8}**	0.144	1.734	0.08	0.238	0.294	0.77
56	rs67736073	9	137,932,302	137,965,157	T	C	0.150	5.682	**1.33×10^{-8}**	0.147	5.795	**6.84×10^{-9}**	0.194	0.352	0.72	0.102	0.226	0.82
57	rs1114148	10	67,521,802	67,548,278	T	C	0.189	5.674	**1.40×10^{-8}**	0.156	5.384	7.30×10^{-8}	0.666	1.469	0.14	0.245	1.222	0.22
58	rs1124372	10	77,537,562	77,660,164	A	G	0.730	5.015	5.30×10^{-7}	0.720	5.539	**3.05×10^{-8}**	0.858	−1.715	0.09	0.854	1.078	0.28
59	rs2771265	10	93,791,409	94,134,467	T	C	0.327	−5.503	**3.74×10^{-8}**	0.343	−5.393	6.94×10^{-8}	0.095	−1.023	0.31	0.255	−0.522	0.60
60	rs11192260	10	106,563,924	106,830,537	T	C	0.221	−5.571	**2.54×10^{-8}**	0.212	−5.444	5.20×10^{-8}	0.370	−1.213	0.23	0.092	−0.239	0.81
60	rs7914674	10	106,563,924	106,830,537	T	C	0.755	5.515	**3.49×10^{-8}**	0.789	5.694	**1.24×10^{-8}**	0.252	0.127	0.90	0.894	0.045	0.96
61	rs4350350	11	28,591,168	28,709,434	T	C	0.391	−5.813	**6.13×10^{-9}**	0.380	−5.444	5.20×10^{-8}	0.564	−2.454	0.01	0.325	0.435	0.66
61	rs11529859	11	28,642,381	28,695,181	T	C	0.724	5.278	1.31×10^{-7}	0.713	5.579	**2.41×10^{-8}**	0.862	−0.218	0.83	0.877	−0.484	0.63
62	rs488769	11	57,369,008	57,681,828	A	C	0.658	−8.577	**9.72×10^{-18}**	0.656	−8.815	**1.20×10^{-18}**	0.653	−0.842	0.40	0.865	1.328	0.18
63	rs559566	11	64,567,047	64,584,231	A	G	0.548	−5.665	**1.47×10^{-8}**	0.560	−5.786	**7.19×10^{-9}**	0.364	0.070	0.94	0.612	−1.148	0.25
64	rs7106434	11	112,826,867	113,034,787	T	C	0.462	8.125	**4.46×10^{-16}**	0.450	8.410	**4.09×10^{-17}**	0.593	−0.745	0.46	0.674	2.180	0.03
64	rs2186710	11	112,826,867	113,034,787	C	G	0.540	−7.992	**1.33×10^{-15}**	0.545	−8.456	**2.78×10^{-17}**	0.501	1.327	0.18	0.328	−1.896	0.06
65	rs10842260	12	24,166,426	24,225,819	A	G	0.467	−5.210	1.89×10^{-7}	0.466	−5.577	**2.44×10^{-8}**	0.510	0.554	0.58	0.284	0.305	0.76
66	rs2292996	12	103,447,647	103,556,972	T	C	0.476	−5.732	**9.92×10^{-9}**	0.496	−5.817	**6.00×10^{-9}**	0.191	−0.355	0.72	0.382	−0.397	0.69
67	rs816363	12	117,649,880	117,700,047	C	G	0.580	−5.870	**4.37×10^{-9}**	0.597	−5.762	**8.29×10^{-9}**	0.397	−1.415	0.16	0.334	0.270	0.79
68	rs16948230	12	118,585,698	118,888,131	A	G	0.858	−6.637	**3.20×10^{-11}**	0.855	−6.522	**6.95×10^{-11}**	0.894	−1.338	0.18	0.943	−0.197	0.84
68	rs61946067	12	118,585,698	118,888,131	T	C	0.862	−6.119	**9.44×10^{-10}**	0.855	−6.536	**6.34×10^{-11}**	0.960	0.960	0.34	0.943	−0.562	0.57
69	rs1373273	13	53,865,141	54,039,629	A	C	0.565	−5.838	**5.28×10^{-9}**	0.566	−5.583	**2.37×10^{-8}**	0.544	−0.938	0.35	0.616	−2.310	0.02
70	rs17084460	13	69,561,090	69,687,825	A	T	0.916	5.714	**1.11×10^{-8}**	0.919	5.623	**1.88×10^{-8}**	0.858	0.985	0.32	0.963	0.510	0.61
70	rs7333625	13	69,561,090	69,687,825	A	T	0.900	5.203	1.96×10^{-7}	0.910	5.680	**1.34×10^{-8}**	0.740	−1.397	0.16	0.956	0.790	0.43
71	rs11628299	14	42,036,322	42,697,579	A	G	0.448	5.679	**$1.36\times^{-8}$**	0.427	5.708	**1.14×10^{-8}**	0.760	0.608	0.54	NA	NA	NA
72	rs57167554	14	47,238,606	47,448,072	A	G	0.529	−6.654	**2.86×10^{-11}**	0.524	−6.823	**8.91×10^{-12}**	0.659	−0.022	0.98	0.207	−0.753	0.45
72	rs2899991	14	47,238,606	47,448,072	T	C	0.470	6.617	**3.67×10^{-11}**	0.475	6.840	**7.91×10^{-12}**	0.339	−0.153	0.88	0.793	0.655	0.51
73	rs7141058	14	69,429,386	69,765,644	A	G	0.472	−5.845	**5.08×10^{-9}**	0.480	−5.987	**2.14×10^{-9}**	0.398	−0.154	0.88	0.205	−0.380	0.70
74	rs11552464	14	103,229,696	103,387,971	T	G	0.838	−6.427	**1.31×10^{-10}**	0.834	−6.009	**1.86×10^{-9}**	0.937	−2.548	0.01	0.578	−0.004	1.00

https://doi.org/10.1038/s41588-024-01707-9

Table 1 (continued) | GWS loci associated with PTSD in the multi-ancestry and European PGC-PTSD Freeze 3 data

Locus[a]	Lead SNP[b]	Chr	Start	Stop	A1	A2	Multi-ancestry[c](150,793 cases,1,130,197 controls)			EA[c](137,136 cases,1,085,746 controls)			AA[c](11,560 cases,39,474 controls)			LAT[c](2,064 cases,4,953 controls)		
							A1 Freq	*Z* score	*P* value[d]	A1 Freq	*Z* score	*P* value[d]	A1 Freq	*Z* score	*P* value[d]	A1 Freq	*Z* score	*P* value[d]
74	rs10132977	14	103,230,005	103,387,971	T	C	0.203	6.074	**1.25×10^{-9}**	0.174	6.227	**4.74×10^{-10}**	0.605	0.328	0.74	0.442	−0.092	0.93
75	rs7170398	15	77,995,949	78,146,382	T	C	0.400	6.583	**4.62×10^{-11}**	0.412	6.459	**1.05×10^{-10}**	0.254	1.242	0.21	0.307	0.528	0.60
76	rs17514846	15	91,412,850	91,429,042	A	C	0.484	−6.925	**4.36×10^{-12}**	0.459	−6.870	**6.44×10^{-12}**	0.801	−1.151	0.25	*NA*	*NA*	*NA*
77	rs1861188	16	6,310,645	6,345,984	A	G	0.654	−5.733	**9.88×10^{-9}**	0.683	−5.514	**3.50×10^{-8}**	0.228	−1.544	0.12	0.680	−0.358	0.72
78	rs6416794	16	51,172,677	51,202,778	T	C	0.234	5.572	**2.52×10^{-8}**	0.214	5.252	1.51×10^{-7}	0.501	1.474	0.14	0.140	1.405	0.16
79	rs12930480	16	52,232,367	52,327,267	A	C	0.821	5.837	**5.30×10^{-9}**	0.811	5.216	1.82×10^{-7}	0.950	2.459	0.01	0.923	1.841	0.07
80	rs7200432	16	60,644,510	60,745,208	A	G	0.306	5.121	3.03×10^{-7}	0.306	5.456	**4.87×10^{-8}**	0.311	−0.573	0.57	0.249	0.049	0.96
81	rs7224932	17	30,173,581	30,571,416	C	G	0.165	−5.778	**7.55×10^{-9}**	0.165	−5.599	**2.16×10^{-8}**	0.175	−1.418	0.16	0.148	−0.312	0.75
81	rs143133717	17	30,173,581	30,571,416	T	C	0.130	−5.511	**3.56×10^{-8}**	0.139	−5.771	**7.87×10^{-9}**	0.033	0.115	0.91	0.049	−0.154	0.88
82	rs199526	17	43,460,181	44,865,603	C	G	0.212	6.820	**9.11×10^{-12}**	0.211	6.414	**1.42×10^{-10}**	0.193	1.927	0.05	0.482	1.609	0.11
82	rs2684641	17	43,460,181	44,865,603	A	G	0.824	−6.253	**4.03×10^{-10}**	0.820	−6.646	**3.01×10^{-11}**	0.850	0.450	0.65	0.910	−0.141	0.89
83	rs73338706	17	65,822,573	66,098,979	T	C	0.761	−6.435	**1.24×10^{-10}**	0.789	−6.524	**6.84×10^{-11}**	0.406	−0.512	0.61	0.671	−0.399	0.69
84	rs74515851	17	73,431,367	73,497,272	A	G	0.044	−5.730	**1.00×10^{-8}**	0.046	−5.323	1.02×10^{-7}	0.017	−2.326	0.02	NA	NA	NA
85	rs7243332	18	26,570,584	26,611,564	A	G	0.666	−5.602	**2.12×10^{-8}**	0.680	−5.591	**2.26×10^{-8}**	0.455	−1.043	0.30	0.723	0.431	0.67
86	rs9954874	18	42,843,373	42,843,373	T	C	0.594	5.715	**1.10×10^{-8}**	0.573	5.369	7.91×10^{-8}	0.898	1.723	0.08	0.641	1.152	0.25
87	rs4632195	18	50,555,225	51,055,069	T	C	0.524	7.064	**1.62×10^{-12}**	0.522	7.029	**2.07×10^{-12}**	0.561	1.030	0.30	NA	NA	NA
88	rs896686	18	53,072,319	53,464,917	T	G	0.839	6.232	**4.60×10^{-10}**	0.830	6.195	**5.82×10^{-10}**	0.958	0.820	0.41	0.948	0.584	0.56
89	rs7408312	19	18,412,122	18,444,809	T	G	0.440	−5.885	**3.98×10^{-9}**	0.454	−6.072	**1.26×10^{-9}**	0.198	−0.133	0.89	0.690	−0.102	0.92
90	rs13037326	20	44,680,412	44,747,947	T	C	0.250	5.724	**1.04×10^{-8}**	0.262	5.590	**2.27×10^{-8}**	0.074	0.642	0.52	0.152	1.806	0.07
90	rs6032660	20	44,680,853	44,749,251	A	G	0.763	−5.704	**$1.17\times^{-8}$**	0.751	−5.744	**9.23×10^{-9}**	0.931	0.059	0.95	0.850	−1.888	0.06
91	rs1378559	X	21,074,049	21,696,222	T	C	0.852	5.539	**3.05×10^{-8}**	0.846	5.609	**2.04×10^{-8}**	0.978	−0.484	0.63	0.957	1.178	0.24
92	rs10284205	X	24,914,760	24,927,706	T	C	0.591	−5.567	**2.59×10^{-8}**	0.587	−5.513	**3.53×10^{-8}**	0.705	−0.999	0.32	0.605	−0.048	0.96
93	rs1320317	X	117,333,327	117,339,104	T	C	0.050	−5.328	9.94×10^{-8}	0.031	−5.519	**3.40×10^{-8}**	0.642	0.408	0.68	0.028	−0.108	0.91
94	rs112052534	X	130,428,965	130,432,493	A	G	0.696	−5.929	**3.05×10^{-9}**	0.685	−5.971	**2.35×10^{-9}**	0.930	−0.881	0.38	0.861	0.454	0.65
95	rs2266850	X	149,791,188	149,798,641	C	G	0.478	5.385	7.26×10^{-8}	0.492	5.678	**1.36×10^{-8}**	0.089	−0.219	0.83	0.352	−0.958	0.34

[a]Loci number designations used in manuscript and gene-mapping tables. [b]Where leading marker varied between EA and multi-ancestry, results for both leading markers are shown. [c]Results highlighted in color indicate leading SNPs for a specific locus and ancestry. [d]Meta-analysis effect estimates were tested for significance using two-sided *z* tests. Results bolded were GWS ($P<5\times10^{-8}$). Chr, chromosome; Start, locus start p in base pairs (GR37 Human Genome Build/h19 coordinates); Stop, locus stop position; A1, coded allele (effects and allele frequencies are coded in terms of copies of this allele); A2, noncoded allele; A, adenosine; C, cytosine; G, guanidine; T, thymidine; A1 Freq, frequency of allele 1.

https://doi.org/10.1038/s41588-024-01707-9

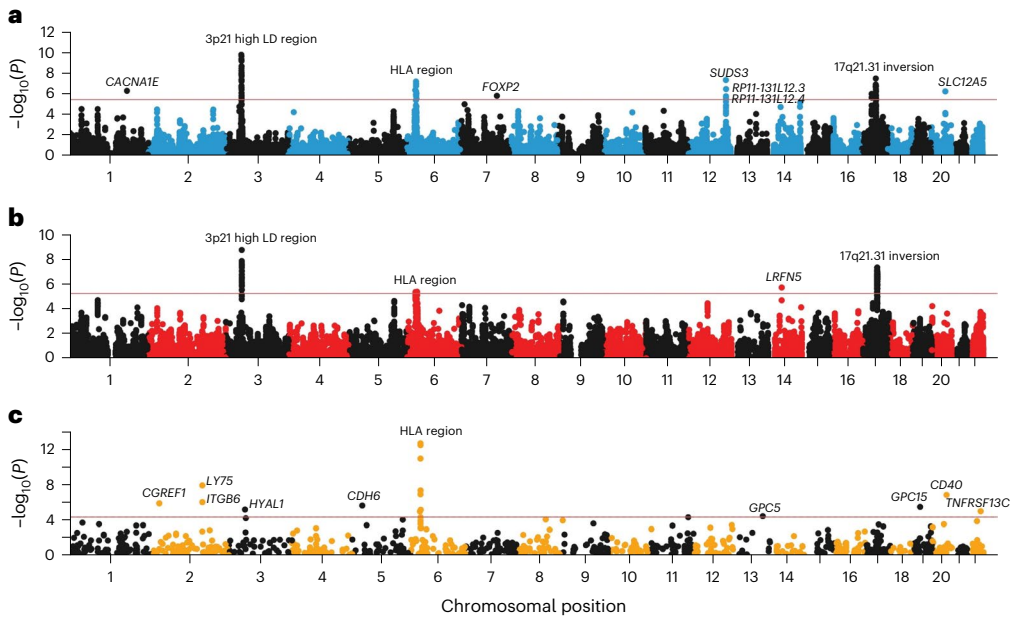

Fig. 3 | Manhattan plots of PTSD associations in multi-omic analyses. **a**,**b**, Gene expression data from 13 brain tissue types and the pituitary were used to conduct TWAS identifying nine loci with differential expression between PTSD cases and controls (**a**) and eQTL SMR identifying four loci where gene expression has putative causal effects on PTSD (**b**). **c**, Blood pQTL SMR identifies 16 blood proteins whose abundance has a putative causal effect on PTSD. The *y* axis refers to $-\log_{10}(P)$ from two-sided *z* tests for TWAS, two-sided chi-square tests for eQTL SMR and two-sided chi-square tests for pQTL SMR. The horizontal red bars indicate gene-wide significance ($P < 0.05/14{,}935$ for TWAS, $P < 0.05/9{,}903$ for eQTL SMR and $P < 0.05/1{,}209$ for pQTL SMR). Significant findings are labeled.

(Supplementary Table 13 and Supplementary Fig. 7). Of these, 52 were distinct from the genes implicated by the gene mapping of individual SNPs within GWS loci. These notably include *DRD2*, which has been thoroughly investigated in the context of psychiatric disorders and is a significant GWAS locus for multiple psychiatric disorders including schizophrenia (SCZ)[32] (see Supplementary Note and Supplementary Table 14 for further investigation of conditionally independent SNPs within these 52 genes).

MAGMA gene-set analysis of 15,483 pathways and gene ontology (GO) terms from Molecular Signatures Database (MSigDB)[33] identified 12 significant GO terms. Significant terms were related to the development and differentiation of neurons (for example, go_central_nervous_system_development, $P = 2.0 \times 10^{-7}$), the synaptic membrane (for example, go_postsynaptic_membrane, $P = 6.9 \times 10^{-7}$), gene regulation (for example, go_positive_regulation_of_gene_expression, $P = 1.0 \times 10^{-6}$) and nucleic acid binding ($P = 1.52 \times 10^{-6}$; Extended Data Fig. 3 and Supplementary Table 15).

MAGMA gene-tissue analysis of 54 tissue types showed PTSD gene enrichment in the brain (most notably in cerebellum, but also cortex, hypothalamus, hippocampus and amygdala) and in the pituitary, with enrichment found across all 13 examined brain regions (Extended Data Fig. 4). Cell-type analysis conducted in midbrain tissue data[34] identified GABAergic neurons, GABA neuroblasts and mediolateral neuroblast type 5 cell types as having enriched associations above other brain cell types tested ($P < 0.05/268$; Extended Data Fig. 5). GABAergic neurons remained significant ($P = 4.4 \times 10^{-5}$) after stepwise conditional analysis of other significant cell types.

Multi-omic investigation of PTSD

To gain insights into which particular genes in enriched brain tissues were contributing to PTSD, we conducted a combination of a transcriptome-wide association study (TWAS)[35] and summary-based Mendelian randomization (SMR) analyses[36] using GTEx brain tissue data based on the EA GWAS summary data. TWAS identified 25 genes within 9 loci with Bonferroni-significantly different genetically regulated expression levels between PTSD cases and controls ($P < 0.05/14{,}935$ unique genes tested; Fig. 3a, Supplementary Fig. 8 and Supplementary Table 16). SMR identified 26 genes within four loci whose expression levels were putatively causally associated with PTSD ($P < 0.05/9{,}003$ unique genes tested; Fig. 3b and Supplementary Table 17). Many of these genes have been previously implicated in PTSD[37] and other psychiatric disorders (for example, *CACNA1E*, *CRHR1*, *FOXP2*, *MAPT* and *WNT3*). Notably, the 3p21.31 (including *RBM6*, *RNF123*, *MST1R*, *GMPPB* and *INKA1*), 6p22.1 (including *ZCAN9* and *HCG17*) and 17q21.31 (including *ARHGAP27*, *ARL17A*, *CRHR1*, *MAPT*, *FAM215B*, *LRRC37A2*, *PLEKHM1* and *SPPL2C*) regions contained >10 putative causal genes each.

Among the GTEx tissues with the most TWAS and SMR signals was the dorsolateral prefrontal cortex (dlPFC). To gain insight into cell-type resolution, we conducted MAGMA for cell-type-specific markers of dlPFC and cell-type-specific SMR. MAGMA showed significant enrichment of dlPFC inhibitory and excitatory neurons, but also of oligodendrocytes and oligodendrocyte precursor cells (Supplementary Table 18), while the SMR analyses identified cell-type-specific signals for eight genes (*KANSL1*, *ARL17B*, *LINC02210-CRHR1*, *LRRC37A2*, *ENSG00000262633*, *MAPT*, *ENSG00000273919* and *PLEKHM1*) over three loci (six of eight from 17q21.31) and all cell types ($P < 0.05/1{,}885$ unique genes tested) whose expression levels were potentially causally associated with PTSD (Supplementary Table 19). The top gene, *KANSL1*, was significant in all cell types.

Given previously reported associations between blood-based protein levels and PTSD[38,39], we performed protein quantitative trait loci (pQTL) SMR[36] analysis for PTSD using data from the UK Biobank (UKB) Pharma Proteomics Project[40] ($n = 54{,}306$ samples and $n = 1{,}209$ proteins). We identified 16 genes within 9 loci whose protein levels were significantly associated with PTSD ($P < 0.05/1{,}209$ and $P_{HEIDI} > 0.05$; Fig. 3c and Supplementary Table 20), including members of the tumor necrosis factor (TNF) superfamily (for example, *CD40* and *TNFRSF13C*), implicating TNF-related immune activation in PTSD.

Gene prioritization

One research objective was to identify the genes with the greatest evidence of being responsible for the associations observed at each

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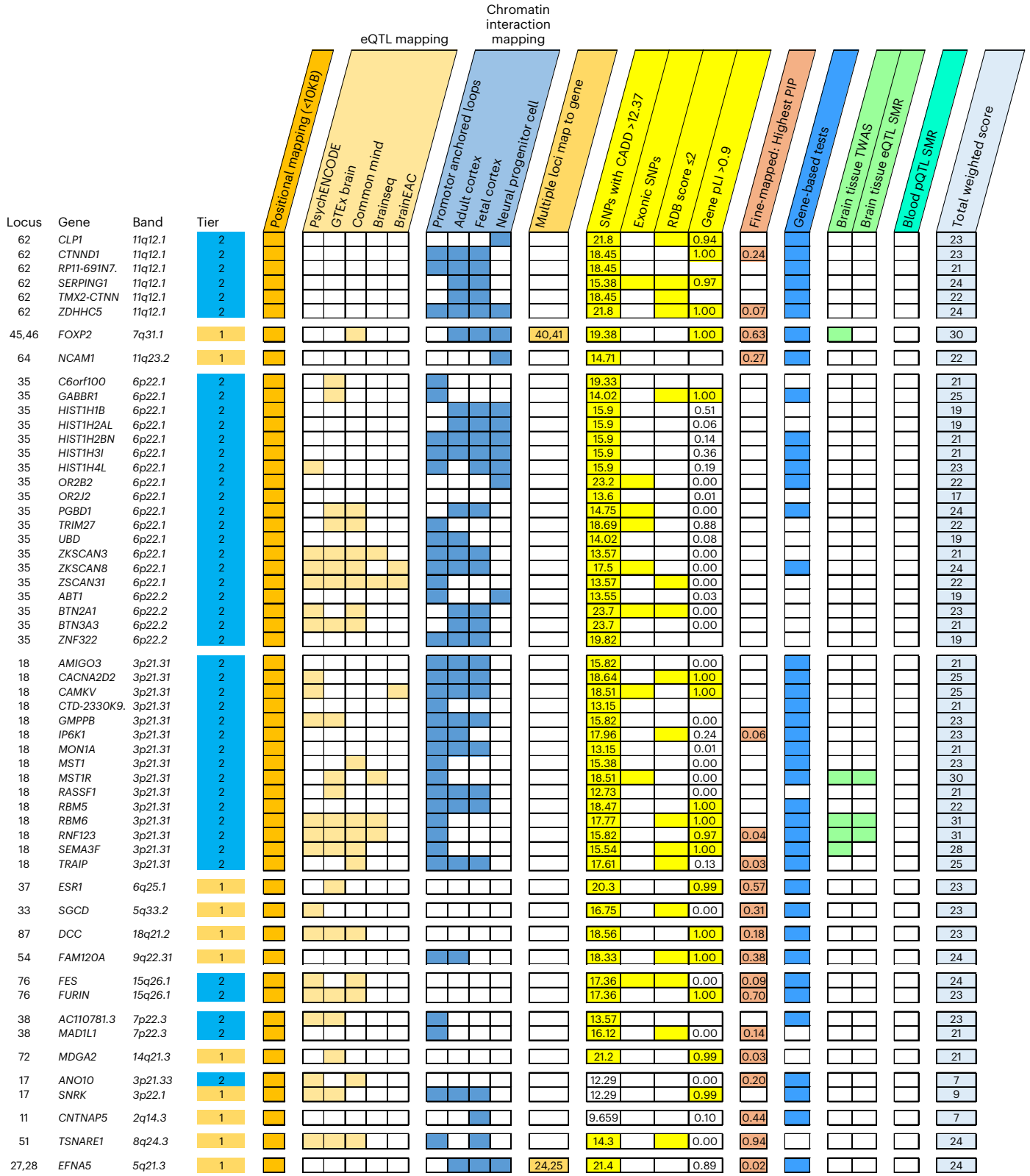

Fig. 4 | Gene prioritization in PTSD loci. Summary of evidence categories of prioritized genes (tier 1 or tier 2) for the top 20% of PTSD loci (as ranked by leading SNP *P* value). Locus number, prioritized genes within the locus, gene locations (in terms of cytogenic band) and gene tier ranks (tier 1, orange; tier 2, blue) are indicated on the left. Categories of evidence are grouped and colored according to the domain they belong to. CADD scores, pLI scores and fine-mapping PIPs are written within their respective squares. The total weighted scores taken across all nine evidence categories are shown on the rightmost squares. PIP, posterior importance probability.

identified PTSD locus. Following recent research methods[41], we prioritized genes based on weighted sum of evidence scores taken across the functional annotation and post-GWAS analyses (Fig. 1b). Based on the absolute and relative scores of genes within risk loci, we ranked genes into tier 1 (greater likelihood of being the causal risk gene) and tier 2 (prioritized over other GWAS-implicated genes, but lower likelihood

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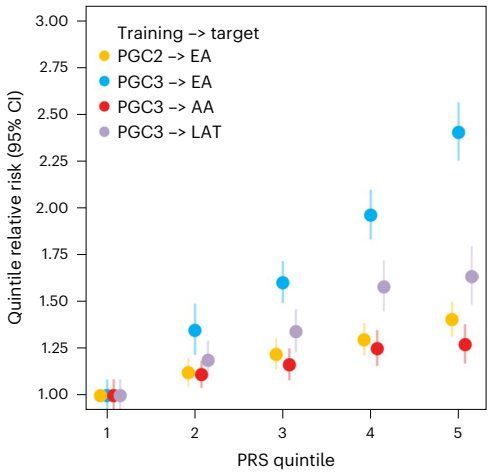

Fig. 5 | PRS analysis for PTSD across different datasets and ancestries. PGC-PTSD Freeze 2 and Freeze 3 EA-based PRS predictions into independent samples of different ancestries. The *y* axis represents PTSD risk relative to the lowest quintile of PRS with 95% CIs. For EA, predictions based on Freeze 3 training data (n = 10,334 cases and n = 55,504 controls; blue circles) demonstrate a significant performance increase compared to predictions based on the previous Freeze 2 training GWAS[11] (yellow circles). Based on Freeze 3 EA training data, EA individuals in the highest quintile of PRS have 2.40-fold (95% CI = (2.26, 2.56)) the risk of PTSD relative to individuals in the lowest quintile PRS (blue circles). Lower prediction accuracies are found for individuals of AA (n = 10,151 cases and n = 22,420 controls; red circles) and LAT (n = 5,346 cases and n = 10,821 controls; purple circles), indicating poor PRS transferability across ancestries.

than tier 1 of being the causal gene). In total, 75% of loci contained prioritized genes (tier 1 or tier 2); the remaining loci did not contain any genes over the minimum threshold of evidence (score ≥4) to suggest prioritization. The prioritized genes for the top 20% of loci (ranked by locus *P* value) are shown in Fig. 4. A complete list of scores and rankings for all 415 protein-coding genes mapped to risk loci is available in Supplementary Data 4.

We performed pathway enrichment analysis of the tier 1 genes in SynGO. From tier 1, 11 genes mapped to the set of SynGO annotated genes (*CACNA1E*, *DCC*, *EFNA5*, *GRIA1*, *GRM8*, *LRFN5*, *MDGA2*, *NCAM1*, *OLFM1*, *PCLO* and *SORCS3*). Relative to other brain-expressed genes, tier 1 genes were significantly overrepresented in the synapse (P = 0.0009, q_{FDR} = 0.003), presynapse and postsynapse (P = 0.0086, q_{FDR} = 0.0086 and P = 0.003, q_{FDR} = 0.004, respectively) and four subcategories (Extended Data Fig. 6). By contrast, there was no significant overrepresentation of genes when we applied this test to the entire set of 415 protein-coding genes. Other notable tier 1 genes included *PDE4B* related to synaptic function and TNF-related immune-regulatory genes, including *TANK* and *TRAF3*.

Genetic architecture of PTSD

SNP-based heritability (h^2_{SNP}) estimated by LDSC was 0.053 (s.e. = 0.002, $P = 6.8 \times 10^{-156}$). Although previous reports suggested sex-specific differences in PTSD[11], no significant differences were found (P = 0.13), and r_g between male and female subsets was high (r_g = 0.98, s.e. = 0.05, $P = 1.2 \times 10^{-98}$; Supplementary Table 5). MiXeR estimated 10,863 (s.e. = 377) influential variants and discoverability of 7.4×10^{-6} (s.e. = 2.2×10^{-7}; Supplementary Table 3), indicating a genetic architecture comparable to other psychiatric disorders[42].

Partitioned heritability across 28 functional categories identified enrichment in histone markers (H3K9ac peaks: 6.3-fold enrichment, s.e. = 1.12, $P = 3.11 \times 10^{-6}$; H3K4me1: 1.5-fold enrichment, s.e. = 0.14, $P = 3.3 \times 10^{-4}$; Supplementary Table 21) and in evolutionary constrained regions across 29 Eutherians (18.37-fold enrichment, s.e. = 1.18, $P = 1.29 \times 10^{-17}$). This is consistent with findings for multiple other psychiatric disorders but has not been previously identified in PTSD[42].

Contextualization of PTSD among psychiatric disorders

We measured the genetic overlap between PTSD and other psychiatric disorders using the most recent available datasets[32,43–52]. We observed moderate to high positive r_g between PTSD and other psychiatric disorders (Extended Data Fig. 7a). To gain further insights into this overlap, we used MiXeR to quantify the genetic overlap in causal variation between PTSD and bipolar disorder (BPD), MDD and SCZ (Extended Data Fig. 7b). The strong majority (79–99%) of the variation influencing PTSD risk also influenced these disorders (Extended Data Fig. 7b and Supplementary Tables 22 and 23). Similar to r_g, PTSD had the highest fraction of concordant effect directions with MDD (among the shared variation; 87% concordant, s.e. = 2%), significantly higher than the directional concordance with BPD (67%, s.e. = 1%) and SCZ (65%, s.e. = 0.5%).

While our results indicate an overall strong r_g between PTSD and MDD (r_g = 0.85, s.e. = 0.008, $P < 2 \times 10^{-16}$), the correlation between PTSD and MDD varied significantly across PTSD subsets, with the most homogeneously assessed subset, MVP, showing the lowest correlation, and the biobank subset being most strongly associated (Supplementary Table 24). Furthermore, to evaluate if specific genetic regions differ substantially from genome-wide estimates, we used LAVA[53] to estimate the local h^2_{SNP} and r_g of PTSD and MDD across the genome, as partitioned into 2,495 approximately independent regions (Supplementary Table 25). Local h^2_{SNP} was significant ($P < 0.05/2{,}495$) for both PTSD and MDD in 141 regions. Of these, local r_g was significant ($P < 0.05/141$) in 40 regions, all in the positive effect direction, where the mean local r_g was 0.57 (s.d. = 0.24). In addition, we assessed the local r_g between PTSD and MDD specifically for the 76 autosomal GWS EA loci (Supplementary Table 26). While LAVA identified 20 significantly correlated loci ($r_g < 6.58 \times 10^{-4}$), there was also evidence for PTSD loci lacking evidence for correlation with MDD (Supplementary Figs. 9 and 10 showcase 6 selected loci with low and high r_g).

Contextualization of PTSD across other phenotype domains

Considering all 1,114 traits with SNP-based heritability $z > 6$ available from the Pan-UKB[54] analysis, we observed Bonferroni-significant r_g of PTSD with 73% of them (Supplementary Table 27). Examining the extremes of estimates observed, the top positive r_g was with sertraline prescription (r_g = 0.88, $P = 3.25 \times 10^{-20}$), a medication frequently prescribed for PTSD and other internalizing disorders[55]. Other leading associations included medication poisonings (for example, 'poisoning by psychotropic agents' r_g = 0.88, $P = 3.92 \times 10^{-20}$), which could support a link with accidental poisonings or self-harm behaviors[56,57]. Converging with epidemiologic studies, there were correlations with gastrointestinal symptoms[58] (for example, 'nausea and vomiting' r_g = 0.80, $P = 2.39 \times 10^{-16}$), mental health comorbidities[59] (for example, 'probable recurrent major depression (severe)' r_g = 0.87, $P = 1.18 \times 10^{-18}$; 'recent restlessness' r_g = 0.86, $P = 4.21 \times 10^{-54}$), chronic pain[60] (multisite chronic pain r_g = 0.63, $P = 7.5 \times 10^{-301}$) and reduced longevity[61–63] ('mother's age at death' r_g = −0.51, $P = 7.6 \times 10^{-27}$).

Drug target and class analysis

We extended the MAGMA gene-set analysis to investigate 1,530 gene sets comprising known drug targets (Supplementary Table 28). We identified one drug (stanozolol, an anabolic steroid) significantly enriched for targets associated with PTSD ($P = 1.62 \times 10^{-5}$). However, stanozolol has only two target genes in our analyses (*ESR1* and *JUN*) and likely reflects the strong association of *ESR1* with PTSD in gene-level analyses ($P = 8.94 \times 10^{-12}$).

We further examined whether high-ranking drug targets were enriched for 159 drug classes defined by Anatomical Therapeutic Chemical (ATC) codes. We identified two broad classes where drugs were significantly enriched for association in drug target analyses

(Supplementary Table 29). These were opioid drugs (ATC code N02A, $P = 2.75 \times 10^{-4}$) and psycholeptics (ATC code N05, $P = 3.62 \times 10^{-5}$), particularly antipsychotics (ATC code N05A, $P = 3.55 \times 10^{-7}$). However, sensitivity analyses limited to drugs with ten or more targets identified no significant drug target sets or drug classes.

Polygenic predictive scoring

We evaluated the predictive accuracy of PRS based on PTSD Freeze 3 in a set of MVP holdout samples (Fig. 5). In EA holdouts, risk was significantly different across the range of PTSD PRS. For example, individuals in the highest quintile of PTSD PRS had 2.4 times the relative risk of PTSD (log relative risk s.e. = 0.032; 95% confidence interval (CI) = (2.25, 2.56); $P = 1.16 \times 10^{-167}$) than individuals in the lowest quintile. PRS explained 6.6% of the phenotypic variation in PTSD (Nagelkerke's R^2 transformed to the liability scale at 15% population and sample prevalence), representing a major improvement over PRS based on Freeze 2. In contrast, among AA holdout samples, PRS explained only 0.9% (liability scale) of the variation in PTSD, consistent with previous work suggesting that AA PRS based on EA data lag behind in prediction[64].

Discussion

In the largest PTSD GWAS to date, we analyzed data from over 1 million individuals and identified a total of 95 independent risk loci across analyses, a fivefold increase over the most recent PTSD GWAS[11–13]. Compared to previous PTSD GWAS, we confirmed 14 of 24 loci and identified 80 new PTSD loci. Variant discovery in psychiatric GWAS follows a sigmoid curve, rapidly increasing once sample size passes a given threshold. This analysis passes that inflection point in PTSD[65], thus representing a major milestone in PTSD genetics. Moreover, by leveraging complementary research methodologies, our findings provide new functional insights and a deeper characterization of the genetic architecture of PTSD.

Tissue and cell-type enrichments revealed the involvement of cerebellum, in addition to other traditionally PTSD-associated brain regions, and interneurons in PTSD risk. Structural alterations in the cerebellum are associated with PTSD[66], and large postmortem transcriptomic studies of PTSD consistently reveal differential expression of interneuron markers in prefrontal cortical tissue and amygdala nuclei[67–69]. We used a combination of TWAS and SMR to probe the causal genes operating within the enriched tissues and cell types with brain transcriptomic data. The identified signals were concentrated in some GWAS loci like 17q21.31 whose inversion region is associated with a range of psychiatric phenotypes and linked to changes in brain structure and function. *KANSL1*, *ARL17B*, *LINC02210-CRHR1* (encoding a fusion protein with CRHR1) and *LRRC37A2* were the top causal genes in both neuronal and nonneuronal cell types. *KANSL1* has a critical role in brain development. Furthermore, the first single-cell transcriptomic study of PTSD confirmed neuronal, excitatory and inhibitory alterations in 17q21.31, with top alterations in *ARL17B*, *LINC02210-CRHR1* and *LRRC37A2*, while also emphasizing the involvement of immune and glucocorticoid response in neurons[70].

Notably, although PTSD risk in epidemiological studies is higher in women than men[71], here we found no sex differences in heritability. Five loci on the X chromosome are associated with the disorder. Our finding that the estrogen receptor (*ESR1*) gene was identified in GWAS, as well as observations of differential effects of estrogen levels on a variety of PTSD symptoms[72,73], suggests the importance of further analyses of *ESR1* as a potential mediator of observed sex differences.

Our analyses prioritized 43 genes as tier 1 (likely causal) based on weighted sum of evidence scores taken across the functional annotation and post-GWAS analyses. These genes can broadly be classified as neurotransmitter and ion channel synaptic plasticity modulators (for example, *GRIA1*, *GRM8* and *CACNA1E*), developmental, axon guidance and transcription factors (for example, *FOXP2*, *EFNA5* and *DCC*), synaptic structure and function genes (for example, *PCLO*, *NCAM1* and *PDE4B*) and endocrine and immune regulators (for example, *ESR1*, *TRAF3* and *TANK*). Furthermore, many additional genes with known function in related pathways were GWS and met tier 2 prioritization criteria (for example, *GABBR1*, *CACNA2D2*, *SLC12A5*, *CAMKV*, *SEMA3F*, *CTNND1* and *CD40*). Together, these top genes show a remarkable convergence with neural networks, synaptic plasticity and immune processes implicated in psychiatric disease. Furthermore, *CRHR1* (refs. 70,74), *WNT3* (refs. 75,76) and *FOXP2* (refs. 77,78), among other genes, are implicated in preclinical and clinical work related to stress, fear and threat-processing brain regions thought to underlie the neurobiology of PTSD. These findings largely support existing mechanistic hypotheses, and it will be important to examine how these genes and pathways function in already identified stress-related neural circuits and biological systems. Furthermore, while some of the prioritized genes are largely within pathways currently indicated in PTSD, many of the specific genes and encoded proteins were not previously established and warrant further investigation. Additionally, many genes and noncoding RNAs were not previously identified in any psychiatric or stress-related disorder and offer an important road map for determining the next steps in understanding new mechanisms of vulnerability for post-traumatic psychopathology. Future mechanistic research in preclinical models should examine whether targeting combinations of these genes, for example, via polygenic targeting, epigenetic or knockdown approaches, would have increased power in regulating stress, fear, cognitive dysfunction or other symptoms and behaviors seen in PTSD.

We observed highly shared polygenicity between PTSD and other psychiatric disorders, albeit with effect discordance across the shared variation. In particular, in some cases, we found that the genetic correlation of PTSD with MDD is as high or higher than genetic correlations between different cohorts, with different measures, of PTSD. Thus, our findings corroborate the hypothesis that psychiatric disorders share a substantial amount of risk variation but are differentiated by disorder-specific effect sizes[43]. Across the disorders we assessed, the correlation between PTSD and MDD was highest, in agreement with existing genetic multifactor models of psychopathology that consistently cluster these disorders together[42,79] and concordant with their epidemiologic comorbidity[80]. Evaluation of local patterns of heritability and genetic correlation however indicates disorder-specific risk variation, which will serve as targets for follow up in cross-disorder investigations. We note that as GWAS of psychiatric traits grow in size and power, the field is seeing relatively strong genetic correlations among these traits, as well as with other behavioral and medical traits. This likely reflects, in part, the reality that there is substantial shared genetic variance among these traits, while not excluding the consistent observations that (1) these traits do vary considerably in the magnitude of their genetic correlations, and (2) local genetic correlations reveal even greater genetic heterogeneity among these traits than global genetic correlations alone would lead us to believe. Finally, while PTSD is the most well-understood psychiatric outcome of trauma exposure, it is well-documented that trauma is a risk factor for many different psychiatric disorders, with perhaps depression as the highest risk. Thus, these shared areas of overlap may represent general trauma vulnerability as well.

Despite the high level of overall correlation between PTSD and depression, we also note certain areas of clear distinction. When we examined local genetic correlations between PTSD and depression within all significant loci from the EA PTSD GWAS, we found that there were some regions with significant local heritability for PTSD but not depression, suggestive of PTSD-specific signals. In contrast, we also find other regions with clear shared signals showing local correlation across depression and PTSD, indicating that we have the power to detect shared and distinct local heritability. Together these findings suggest several PTSD-specific loci worthy of further investigation.

Further identification of PTSD genetic loci will provide therapeutic insights[81]. We explored whether genes targeted by specific drugs (and drug classes) were enriched for GWAS signal. These analyses provided tentative support for antipsychotics and opioid drugs—known psychiatric drug classes—and were driven by gene-wise associations with *DRD2* (antipsychotics) and *CYP2D6* (opioids). Atypical antipsychotics may have efficacy in treating severe PTSD, but otherwise, their use is not supported[82]. Similarly, although some observational studies find that chronic opioid use worsens PTSD outcomes[83], there is preclinical work motivating the further study of opioid subtype-specific targeting (for example, partial μ-type opioid receptor (MOR1) agonism, κ-type opioid receptor (KOR1) antagonism) in the treatment of comorbid PTSD and opioid use disorders[84]. Analyses in better-powered datasets may identify drug repositioning opportunities and could use the predicted effect of associated variants on gene expression to indicate whether drug candidates would be beneficial or contraindicated in people with PTSD.

In summary, we report 81 loci associated with PTSD in EA meta-analysis and 85 loci when expanding to cross-ancestry analyses. While these results represent a milestone in PTSD genetics and point to exciting potential target genes, further investment into data collection from underrepresented populations of diverse ancestries is needed for the identification of additional risk variants and to generate equitable and more robust PRS.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41588-024-01707-9.

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AURORA Study

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Methods

Participants and studies

PTSD assessment and DNA collection for GWAS analysis were performed by each study following their protocols. A description of the studies included and the phenotypic and genotyping methods for each study are provided in Supplementary Note and Supplementary Table 1. We complied with relevant ethical regulations for human research. All participants provided written informed consent, and studies were approved by the relevant institutional review boards and the UCSD IRB (protocol 16097×).

EHR studies

A total of ten EHR-based cohorts (not including the MVP, which also contributed data) provided GWAS summary statistics. These cohorts consisted of four US-based sites (Vanderbilt University Medical Center's BioVu, the Mass General Brigham Biobank, Mount Sinai's BioMe and Mayo Clinic's MayoGC) and six non-US sites (iPSYCH from Denmark, FinnGen, HUNT Study from Norway, STR-STAGE from Sweden, UKB and Estonia Biobank). More details on procedures at each site are provided in Supplementary Note. At each site, a broad definition of PTSD cases was defined based on patients having at least one PTSD or other stress disorder code (see Supplementary Note for the list of corresponding International Classification of Diseases (ICD)-9 and ICD-10 codes). All other patients without such a code were defined as controls. From a total of 817,181 participants across all cohorts, this case definition resulted in 78,687 (9.6%) cases based on the broad definition.

Data assimilation

Participants were genotyped on Illumina (n = 84 studies) or Affymetrix genotyping arrays (n = 5 studies; Supplementary Table 1). Studies that provided direct access to prequality control genotype data (n = 64 studies) were deposited on the LISA server for central processing and analysis by the PGC-PTSD analyst. Studies with data-sharing restrictions (n = 24 studies) were processed and analyzed following their own site-specific protocols (Supplementary Table 28) and shared GWAS summary statistics for inclusion in meta-analysis.

Genotype quality control and imputation

Genotype data were processed separately by study. For genotype data processed by the PGC-PTSD analyst, quality control was performed using a uniform set of criteria, as implemented in the RICOPILI[85] pipeline version 2019_Oct_15.001. Modifications were made to the pipeline to allow for ancestrally diverse data and are noted where applicable. For quality control, SNPs with call rates >95%, samples were excluded with call rates <98%, deviation from expected inbreeding coefficient (fhet < −0.2 or >0.2) or a sex discrepancy between reported and estimated sex based on inbreeding coefficients calculated from SNPs on X chromosomes. SNPs were excluded for call rates <98%, a >2% difference in missing genotypes between cases and controls or being monomorphic. Hardy–Weinberg equilibrium was calculated within only in the largest homogenous ancestry group found in the data. SNPs with a Hardy–Weinberg equilibrium $P < 1 \times 10^{-6}$ in controls were excluded.

After quality control, datasets were lifted over to the GRCh37/hg19 human genome reference build. SNP name inconsistencies were corrected, and genotypes were aligned to the strand of the imputation reference panel. Markers with nonmatching allele codes or with excessive minor allele frequency (MAF) difference (>0.15) with the selected corresponding population in the reference data were removed. The pipeline was modified so that only the largest homogenous ancestry group in the data was used for the calculation of MAF. For ambiguous markers, the strand was matched by comparing allele frequencies—if a strand flip resulted in a lower MAF difference between the study and the reference data, the strand was flipped. Ambiguous markers with high MAF (>0.4) were removed. The genome was broken into 132 approximately equal-sized chunks. For each chunk, genotypes were phased using Eagle v2.3.5, and phased genotypes were imputed into the Haplotype Reference Consortium panel[86] using minimac3. Imputed datasets were deposited with the PGC DAC and are available for approved requests.

Studies with data-sharing restrictions followed similar criteria for quality control, as detailed in Supplementary Table 28 and in the references in Supplementary Note. Studies were imputed to either the 1000G phase 3, HRC, SISu panel or a composite panel. GWAS summary data were lifted to the GRCh37 reference build where required. As differences in the imputation panels and genome reference build can result in SNP-level discrepancies between datasets, each set of summary data was examined for correspondence to the centrally imputed data. Multi-allelic SNPs and SNPs with nonmatching allele codes were excluded. Strand ambiguous SNPs with high MAF difference (>20%) from the average frequency calculated in the PGC-PTSD data were flagged and examined for strand correspondence.

Ancestry determination

For studies where the PGC analyst had genotype data access, ancestry was determined using a global reference panel[11] using SNPweights[87]. The ancestry pipeline was shared with external sites to be used where possible. Participants were placed into the three following large groupings: European ancestry (EA; individuals with ≥90% European ancestry), African ancestry (AA; individuals with ≥5% African ancestry, <90% European ancestry, <5% East Asian, Native American, Oceanian and Central-South Asian ancestry; and individuals with ≥50% African ancestry, <5% Native American, Oceanian and <1% Asian ancestry) and Native American ancestry, including individuals from Latin America (LAT; individuals with ≥5% Native American ancestry, <90% European, <5% African, East Asian, Oceanian and Central-South Asian ancestry). Native Americans (individuals with ≥60% Native American ancestry, <20% East Asian, <15% Central-South Asian and <5% African and Oceanian ancestry) were included in LAT. All other individuals were excluded from the current analyses. For the MVP cohort, ancestry was determined using a standard principal components analysis approach where MVP samples were projected onto a principal component (PC) space made from 1000 Genomes Phase 3 (KGP3) samples with known population origins (European (EUR), African (AFR), East Asian (EAS), South Asian (SAS) and American (AMR) populations). EHR cohorts followed their own site-specific ancestry classification protocols.

GWAS

GWAS was performed with stratification by ancestry group and study. Strata were only analyzed if they had a minimum of 50 cases and 50 controls, or alternatively 200 participants total. Where noted (Supplementary Table 2), small studies of similar composition were jointly genotyped so they could be analyzed together as a single unit. For GWAS, the association between each SNP and PTSD was tested under an additive genetic model, using a regression model appropriate to the data structure. The statistical model, covariates and analysis software used to analyze each study are detailed in Supplementary Table 30. In brief, studies of unrelated individuals with continuous (case/control) measures of PTSD were analyzed using PLINK 1.9 (ref. 88) using a linear (logistic) regression model that included five PCs as covariates. For studies that retained related individuals, analyses were performed using methods that account for relatedness. QIMR was analyzed using GEMMA[89] v0.96, including the first five PCs as covariates. RCOG was analyzed using the generalized disequilibrium test[90]. UKBB was analyzed using BOLT-LMM[91] including six PCs, and batch and center indicator variables as covariates. VETS was analyzed using BOLT-LMM including five PCs as covariates. EHR-based studies that included related individuals were analyzed using saddle point

approximation methods to account for case/control imbalances. AGDS and QIM2 were analyzed using SAIGE[92] including four PCs and study-specific covariates. BIOV was analyzed using SAIGE including ten PCs and age of record. ESBB, FING, HUNT and SWED were analyzed using SAIGE including five PCs. UKB2 was analyzed using REGENIE[93] including six PCs, assessment center and genotyping batch covariates. GWAS was additionally performed stratified by sex. For the X chromosome analysis, sex was added as a covariate.

Meta-analysis

Sample-size weighted fixed-effects meta-analysis was performed with METAL[94]. Within each dataset and ancestry group, summary statistics were filtered to MAF ≥1% and imputation information score ≥0.6. Meta-analyses were performed within the EA, AA and LAT ancestry groups. A multi-ancestry meta-analysis was performed as the meta-analysis of the three meta-analyses. GWS was declared at $P < 5 \times 10^{-8}$. Heterogeneity between datasets was tested with the Cochran test. Markers with summary statistics in less than 80% of the total effective sample size were removed from meta-analyses. LDSC[24] intercept was used to estimate the inflation of test statistics related to artifacts rather than genetic signals. The proportion of inflation of test statistics due to the actual polygenic signal (rather than other causes such as population stratification) was estimated as 1 − (LDSC intercept − 1)/(mean observed chi-square − 1).

Regional association plots

Regional association plots were generated using LocusZoom[95] with 1.5-Mb windows around the index variant (unless the locus region was wider than 1.5 Mb, in which case it was the locus region plotted plus an additional buffer to include data up to the recombination region). The LD patterns plotted were based on the 1000 Genomes Phase 3 reference data[96], where a sample ancestry-appropriate subpopulation (EUR, AFR or AMR) was used.

Conditional analysis of significant loci

To determine if there were independent significant SNPs within risk loci, GCTA Conditional and Joint Analysis[26] was performed. Stepwise selection was performed using the --cojo-slct option and default parameters, where UKBB European genotype data were used to model LD structure.

SNP heritability

The h^2_{SNP} of PTSD was estimated using LDSC. LD scores calculated within KGP3 European populations (https://data.broadinstitute.org/alkesgroup/LDSCORE/) were used for the input. Analyses were limited to HapMap 3 SNPs, with the MHC region excluded (chr6: 26–34 million base pairs). SNP-based heritability was also calculated as partitioned across 28 functional annotation categories (https://data.broadinstitute.org/alkesgroup/LDSCORE/) using stratified LDSC[97].

Comparisons of genetic architecture

We used univariate MiXeR (version 1.3)[22,23] to contrast the genetic architecture of phenotypes. MiXeR estimates SNP-based heritability and two components that are proportional to heritability—the proportion of nonnull SNPs (polygenicity) and the variance of effect sizes of nonnull SNPs (discoverability). MiXeR was applied to GWAS summary statistics under the default settings with the supplied EA LD reference panel. The results reported for the number of influential variants reflect the number of SNPs necessary to explain 90% of SNP-based heritability. Bivariate MiXeR was used to estimate phenotype-specific polygenicity and the shared polygenicity between phenotypes. Goodness of fit of the MiXeR model relative to simpler models of polygenic overlap was assessed using Akaike information criterion values. Heritability, polygenicity and discoverability estimates were contrasted between datasets using the z test.

Local genetic correlation analyses

Local h^2_{SNP} and r_g between PTSD and MDD[50] were estimated using LAVA[53]. KGP3 European data were used as the LD reference. Local h^2_{SNP} and r_g were evaluated across the genome, as partitioned into 2,495 approximately equal-sized LD blocks. Local r_g was only evaluated for loci where local heritability was significant ($P < 0.05/2{,}495$) in both phenotypes. Significance of local r_g was based on Bonferroni adjustment for the number of r_g evaluated.

PRS

PRS were calculated in ancestry-stratified MVP holdout samples, based on the EA Freeze 3 PTSD GWAS. GWAS summary statistics were filtered to common (MAF >1%), well-imputed variants (INFO >0.8). Indels and ambiguous SNPs were removed. PRS–continuous shrinkage[98] was used to infer posterior effect sizes of SNPs, using the KGP3 EUR-based LD reference panel supplied with the program, with the global shrinkage parameter set to 0.01, 1,000 MCMC iterations with 500 burn-in iterations and the Markov chain thinning factor set to 5. PRS were calculated using the --score option in PLINK 1.9, using the best-guess genotype data of target samples, where for each SNP the risk score was estimated as the posterior effect size multiplied by the number of copies of the risk allele. PRS were estimated as the sum of risk scores over all SNPs. PRS were used to predict PTSD status under logistic regression, adjusting for five PCs. The proportion of variance explained by PRS for each study was estimated as the difference in Nagelkerke's R^2 between a model containing PRS plus covariates and a model with only covariates.

Functional mapping and annotation

We used the SNP2GENE module in FUMA[25] v1.4.1 (https://fuma.ctglab.nl) to annotate and visualize GWAS results. The complete set of parameters used for FUMA analysis are shown in Supplementary Note. Independent genomic risk loci were identified ($r^2 < 0.6$, calculated using ancestry-appropriate KGP3 reference genotypes). SNPs within risk loci were mapped to protein-coding genes using positional mapping (10-kb window), eQTL mapping (GTEx v8 brain tissue[99], BRAINEAC[100] and CommonMind[101] data sources) and chromatin interaction mapping (PsychENCODE[102] and HiC[103,104] of brain tissue types) methods. Chromatin interactions and eQTLs were plotted in circos plots. SNPs were annotated to functional annotation databases including ANNOVAR[105], CADD[28] and RDB[29].

Newness of risk loci

The start and stop positions of independent risk loci were assessed for positional overlap with existing PTSD loci[11–13]. Loci were declared new if their boundaries did not overlap with a variant reported significant in prior GWAS.

MAGMA gene-based and gene-set analyses

Gene-based association analyses were conducted using MAGMA[31] v1.08. SNPs were positionally mapped (0-kb window) to 19,106 protein-coding genes. The SNP-wide mean model was used to derive gene-level P values, and an ancestry-appropriate KGP3 reference panel was used to model LD. Significance was declared based on Bonferroni adjustment for the number of genes tested. Gene-based association statistics were used in MAGMA for gene-set and gene-property analyses. Gene-set analysis used the MsigDB[33] version 7.0 including 15,483 curated gene sets and GO terms. Gene-property analysis of tissues and tissue subtypes was performed using GTEx v8 expression data, with adjustment for the average expression of all tissues in the dataset. To evaluate cell-type-specific enrichment, the FUMA cell-type module was used, selecting 12 datasets related to the brain (see full list in Supplementary Note). Finally, MAGMA was used to estimate the enrichment of dlPFC cell types in PTSD risk based on the DER21 marker gene list from PsychEncode Consortium Phase 1 resource release[102].

GWAS fine-mapping

Polygenic functionally informed fine-mapping (PolyFun)[30] software was used to annotate our results data with per-SNP heritabilities, as derived from a meta-analysis of 15 UKB traits. PTSD risk loci were fine-mapped using SUSIE[106], with these per-SNP heritabilities used as priors, precomputed UKB-based summary LD information used as the LD reference and locus start and end positions as determined by FUMA. The SUSIE model assumed a maximum of two causal variants.

eQTL and blood pQTL analyses

To test for a joint association between GWAS summary statistics SNPs and eQTL, the SMR method[36], a Mendelian randomization approach, was used. SMR software (version 1.03) was run using the default settings. The European samples of the 1000G were used as a reference panel. Bonferroni multiple-testing correction was applied on SMR *P* value (P_{SMR}). Moreover, a postfiltering step was applied by conducting heterogeneity in dependent instruments (HEIDI) test. The HEIDI test distinguishes the causality and pleiotropy models from the linkage model by considering the pattern of associations using all SNPs significantly associated with gene expression in the *cis*-eQTL region. The null hypothesis is that a single variant is associated with both trait and gene expression, while the alternative hypothesis is that trait and gene expression are associated with two distinct variants. Finally, gene–trait associations based on SMR–HEIDI were defined as the ones for which P_{SMR} met the Bonferroni significance threshold and had $P_{HEIDI} > 0.05$. We conducted a combination of SMR and HEIDI based on the GTEx project's latest (version 8) multitissue *cis*-eQTL databases[99] from 13 brain regions and pituitary tissue that showed significant enrichment in MAGMA/FUMA analyses (see above). We also used cell-type-specific eQTLs in dlPFC for SMR analyses[107]. Finally, we used a blood UKB pQTLs database of 1,463 plasma proteins[40] relying on a very large population (54,306) for SMR/HEIDI analysis to evaluate biomarker potential.

Brain focused TWAS

JEPEGMIX2-P[108] software with default settings was used to conduct TWAS on 13 brain regions and pituitary tissue that showed significant enrichment in MAGMA/FUMA analyses using our PEC-DLPFC GReX model. JEPEGMIX2-P was applied on GWAS summary statistics to estimate gene–trait associations. This method was preferable because it relied on a covariance matrix based on 33k samples compared to other TWAS methods, which use less than 3k samples[109]. To determine significance, a Bonferroni correction threshold for the unique number of genes tested was applied ($P < 0.05/14{,}935$). As a less conservative approach, we also applied FDR at a *q* value threshold of 0.05.

Gene prioritization

Genes within risk loci were prioritized following the general approach previously described[41]. Genes were given prioritization scores based on the weighted sum of evidence across all evidence categories–FUMA positional, eQTL and chromatin interaction mapping; variant and gene annotation scores (CADD, predicted loss of impact (pLI) and RDB scores); positional overlap in fine-mapping; significance in gene-based analyses; brain tissue TWAS, eQTL SMR and pQTL SMR. Weights for each evidence category are provided in Supplementary Table 31. Within a given locus, the evidence scores were compared across genes to identify the most likely causal gene. Genes with scores ≥4 were ranked as either tier 1 (greater likelihood of being the causal risk gene) or tier 2 (lower likelihood of being the causal risk gene) and genes with scores <4 were left unranked. The ranking algorithm is as follows. For a given locus, if there was a gene whose evidence score ≥4 and this gene's score was >20% higher than all other genes in the locus, it was ranked as a tier 1 gene (greater likelihood of being the causal risk gene). Within a locus with a tier 1 gene, other genes with scores between 20% and 50% lower than the tier 1 gene were labeled as tier 2. For loci without a tier 1 gene, all genes with scores ≥4 that were within 50% of the leading gene were ranked as tier 2.

SynGO

PTSD-related genes were tested for overrepresentation among genes related to synaptic terms in the SynGO[110] web interface (https://www.syngoportal.org/). Brain-expressed genes were selected as the background list for the overrepresentation tests. SynGO terms with FDR $q < 0.05$ were considered to be overrepresented.

Drug targeting analyses

Following a previously described approach[111], we analyzed the enrichment of gene-level associations with PTSD in genes targeted by individual drugs. We then examined the enrichment of specific drug classes among these drug–target associations. We obtained gene-level associations using MAGMA[31] v1.08. Variant-level associations were converted to gene-level associations using the 'multi=snp-wise' model, which aggregates *z* scores derived from the lowest and the mean variant-level *P* value within the gene boundary. We set gene boundaries 35 kb upstream and 10 kb downstream of the transcribed regions from build 37 reference data (National Center for Biotechnology Information, available at https://ctg.cncr.nl/software/magma).

We performed drug target analysis using competitive gene-set tests implemented in MAGMA. Drug target sets were defined as the targets of each drug from the Drug–Gene Interaction database DGIdb v.4.2.0 (ref. 112), the Psychoactive Drug Screening Database Ki DB[113], ChEMBL v27 (ref. 114), the Target Central Resource Database v6.7.0 (ref. 115) and DSigDB v1.0 (ref. 116), all downloaded in October 2020. We additionally used the drug target sets to identify targets of drugs of interest from gene-based analyses.

We grouped drugs according to the ATC class of the drug[111]. Results from the drug target analysis were ranked, and the enrichment of each class in the drug target analysis was assessed with enrichment curves. We calculated the area under the enrichment curve and compared the ranks of drugs within the class to those outside the class using the Wilcoxon Mann–Whitney test. Multiple testing was controlled using a Bonferroni-corrected significance threshold of $P < 3.27 \times 10^{-5}$ for drug target analysis and $P < 4.42 \times 10^{-4}$ for drug class analysis, accounting for 1,530 drug sets and 113 drug classes tested.

We initially limited drug target analyses to drugs with two or more targets. However, results suggested this low limit may lead to false positive findings. As a sensitivity analysis, we further limited these analyses to drugs with ten or more targets. Multiple testing was controlled using a Bonferroni-corrected significance threshold of $P < 5.42 \times 10^{-5}$ for drug target analysis and $P < 7.94 \times 10^{-4}$ for drug class analysis, accounting for 923 drug sets and 63 drug classes tested.

Genetic correlations with other phenotypes

Using LDSC, we assessed the r_g of PTSD derived from the PGC meta-analysis conducted in EUR cohorts with traits available from the Pan-UKB analysis conducted in EUR samples. Details regarding the Pan-UKB analysis are available at https://pan.ukbb.broadinstitute.org/. Briefly, Pan-UKB genome-wide association statistics were generated using the SAIGE and included a kinship matrix as a random effect and covariates as fixed effects. The covariates included age, sex, age × sex, age^2, age^2 × sex and the top ten within-ancestry principal components. We limited our analysis to data derived from UKB participants of European descent ($n = 420{,}531$) because of the limited sample size available in the other ancestry groups. Initially, we calculated the SNP-based heritability of phenotypes available from Pan-UKB, retaining only those with SNP-based heritability $z > 6$ (Supplementary Table 25) as recommended by the developers of LDSC[117]. To define traits genetically correlated with PTSD, we applied a Bonferroni correction accounting for the number of tests performed.

Reporting summary
Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability
Summary statistics for PGC-PTSD Freeze 3 will be made available upon publication under the accession ID ptsd2024 via the PGC website (https://pgc.unc.edu/for-researchers/download-results/). Access to study-level summary statistics and genotype data can be applied by using the PGC data access portal (https://pgc.unc.edu/for-researchers/data-access-committee/data-access-portal/).

Code availability
Analysis code is made available at GitHub (https://github.com/nievergeltlab/freeze3_gwas) and Zenodo (https://doi.org/10.5281/zenodo.10182702)[118].

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Acknowledgements
Major financial support for the PTSD-PGC was provided by the National Institute of Mental Health (NIMH; R01MH106595 (to K.C.K., C.M.N., K.J.R. and M.B.S.), R01MH124847 (to C.M.N.) and R01MH124851 (to A.D.B., L.K.D. and K.C.K.)), the Stanley Center for Psychiatric Research at the Broad Institute and Cohen Veterans Bioscience. Statistical analyses were carried out on the NL Genetic Cluster computer (URL) hosted by SURFsara. Genotyping of samples was supported in part through the Stanley Center for Psychiatric Genetics at the Broad Institute of MIT and Harvard. This research has been conducted using the UKB resource under application 41209. This work would not have been possible without the contributions of the investigators who comprise the PGC-PTSD working group, and especially the more than 1,307,247 research participants worldwide who shared their life experiences and biological samples with PGC-PTSD investigators. We thank A.E. Aiello, B. Bradley, A. Gautam,

R. Hammamieh, M. Jett, M.J. Lyons, D. Maurer, M.R. Mavissakalian and the late C.R. Erbes and R.E. McGlinchey for their contributions to this study.

Author contributions

E.G.A., S.-A.B., C.-Y.C., K.W.C., J.R.I.C., N.P.D., L.E.D., K.C.K., A.X.M., R.A.M., C.M.N., R.P., K.J.R. and M.B.S. were the members of the PGC-PTSD writing group. A.B.A., S.B. Andersen, P.A.A., A.E.A.-K., S.B. Austin, E.A., D.B., D.G.B., J.C.B., S. Belangero, C. Benjet, J.M.B., L.J.B., J.I.B., G.B., R.B., A.D.B., J.R.C., C.S.C., L.K.B., J.D., D.L.D., T.d.-C., K.D., G.D., A.D.-K., N.F., L.A.F., A.F., N.C.F., B.G., J.G., E.G., C.F.G., A.G.U., M.A.H., A.C.H., V.H., I.B.H., D.M.H., K. Hveem, M. Jakovljević, A.J., I.J., T.J., K.-I.K., M.L.K., R.C.K., N.A.K., K.C.K., R.K., H.R.K., W.S.K., B.R.L., K.L., I.L., B.L., C.M., N.G.M., K.A.M., S.A.M., S.E.M., D.M., W.P.M., M.W.M., C.P.M., O.M., P.B.M, E.C.N., C.M.N., M.N., S.B.N., N.R.N., P.M.P., A.L.P., R.H.P., M.A.P., B.P., A.P., K.J.R., V.R., P.R.B., K.R., H.R., G.S., S. Seedat, J.S. Seng, A.K.S., S.R.S., D.J.S., M.B.S., R.J.U., U.V., S.J.H.v.R., E.V., J.V., Z.W., M.W., H.W., T.W., M.A.W., D.E.W., C.W., R.M.Y., H.Z., L.A.Z. and J.-A.Z. were the principal investigators or co-principal investigators of contributing studies. A.B.A., P.A.A., A.E.A.-K., S.B. Austin, J.C.B., S. Belangero, C. Benjet, J.M.B., L.J.B., G.B., A.D.B., C.S.C., J.D., T.d.-C., A.F., N.C.F., J.D.F., C.E.F., E.G., C.F.G., M.H., M.A.H., A.C.H., V.H., I.B.H., D.M.H., K. Hveem, T.J., N.A.K., K.C.K., R.K., W.S.K., B.R.L., B.L., C.M., N.G.M., K.A.M., S.A.M., S.E.M., J.M., W.P.M., M.W.M., C.P.M., O.M., P.B.M, E.C.N., C.M.N., M.N., N.R.N., H.K.O., M.A.P., B.P., K.J.R., B.O.R., G.S., M.S., A.K.S., S.R.S., M.H.T., R.J.U., U.V., E.V., J.V., Z.W., M.W., T.W., M.A.W., D.E.W., R.Y., R.M.Y. and L.A.Z. obtained funding for studies. C.A., P.A.A., E.A., D.B., D.G.B., J.C.B., L.B., L.J.B., E.A.B., R.B., A.C.B., A.D.B., S. Børte, L.C., J.R.C., K.W.C., L.K.B., M.F.D., T.d.-C., S.G.D., G.D., A.D.-K., N.F., N.C.F., J.D.F., C.E.F., S.G., E.G., A.G.U., S.B.G., L.G., C.G., V.H., D.M.H., M. Jakovljević, A.J., G.D.J., M.L.K., A.K., N.A.K., N.K., R.K., W.S.K., B.R.L., L.A.M.L., K.L., C.E.L., B.L., J.L.M.-K., S.A.M., P.B.M., H.K.O., P.M.P., M.S.P., E.S.P., A.L.P., M.P., R.H.P., M.A.P., B.P., A.P., B.O.R., A.O.R., G.S., L.S., J.S. Seng, C.M.S., S. Stensland, M.H.T., W.K.T., E.T., M.U., U.V., L.L.v.d.H., E.V., Z.W., Y.W., T.W., D.E.W., B.S.W., S.W., E.J.W., R.Y., K.A.Y. and L.A.Z. were responsible for clinical aspects of studies. O.A.A., P.A.A., S.B. Austin, D.G.B., S. Belangero, L.J.B., R.B., R.A.B., A.D.B., J.R.C., J.M.C.-d.-A., S.Y.C., S.A.P.C., A.M.D., L.K.B., D.L.D., A.E., N.C.F., D.F., C.E.F., S.G., B.G., S.M.J.H., D.M.H., L.M.H., K. Hveem, A.J., I.J., M.L.K., J.L.K., R.C.K., A.P.K., R.K., W.S.K., L.A.M.L., K.L., D.F.L., C.E.L., I.L., B.L., M.K.L., S.M., G.A.M., K.M., A.M., K.A.M., S.E.M., J.M., L.M., O.M., P.B.M., M.N., S.B.N., N.R.N., M.O., P.M.P., M.S.P., E.S.P., A.L.P., M.P., R.H.P., M.A.P., K.J.R., V.R., P.R.B., A. Rung, G.S., L.S., S.E.S., M.S., C.S., S. Seedat, J.S. Seng, D. Silove, J.W.S., S.R.S., M.B.S., A.K.T., E.T., U.V., L.L.v.d.H., M.V.H., M.W., T.W., D.E.W., S.W., K.A.Y., C.C.Z., G.C.Z., L.A.Z. and J.-A.Z. contributed to data collection. A.E.A.-K., A. Batzler, C. Bergner, A. Brandolino, S. Børte, C.C., C.-Y.C., S.A.P.C., J.R.I.C., L.C.-C., B.J.C., S.D., S.G.D., A.D., L.E.D., C.F., M.E.G., B.G., S.B.G., S.D.G., C.G., S.H., E.M.H., K. Hogan, H.H., G.D.J., K.K., P.-F.K., D.F.L., M.W.L., A.L, Y.L., A.X.M., S.M., C.M., D.M., J.M., V.M., E.A.M., M.S.M., C.M.N., G.A.P., M.P., X.-J.Q., A.R., A.L.R., S.S.d.V., C.S., A.S., C.M.S., S. Stensland, J.S.S., J.A.S., F.R.W., B.S.W., Y. Xia, Y. Xiong and C.C.Z. conducted statistical analysis. A.E.A.-K., A. Batzler, M.P.B., S. Børte, C.C., C.-Y.C., J.R.I.C., N.P.D., C.D.P., S.G.D., A.D., H.E., M.E.G., K. Hogan, H.H., K.K., P.-F.K., D.F.L., S.D.L., A.L, A.X.M., G.A.M., D.M., J.M., V.M., E.A.M., G.A.P., A.R., A.S., J.S.S., F.R.W., B.S.W., C.W., Y. Xia, Y. Xiong and C.C.Z. conducted bioinformatics analysis. M.P.B., J.B.-G., M.B.-H., N.P.D., T.d.-C., F.D., A.D., K.D., H.E., L.G., M.A.H., J.J., P.-F.K., S.D.L., J.J.L., I.K., J.M., L.M., K.J.R., B.P.F.R., S.S.d.V., A.S., C.H.V. and D.E.W. conducted genomics studies. M.H. and M.Z were the members of the PGC-PTSD management group.

Competing interests

L.J.B. is listed as an inventor on Issued US Patent 8,080,371, 'Markers for Addiction' covering the use of certain SNPs in determining the diagnosis, prognosis and treatment of addiction. C.-Y.C. and H.R. are employees of Biogen. A.M.D. holds equity in CorTechs Labs and serves on the Scientific Advisory Board of Human Longevity and the Mohn Medical Imaging and Visualization Center. A.M.D. receives funding through research grants with General Electric Healthcare. C.F. was a speaker for Janssen in 2021. I.B.H. is the codirector, Health and Policy at the Brain and Mind Center (BMC) University of Sydney; the BMC operates early intervention youth services at Camperdown under contract to headspace; and is the Chief Scientific Advisor to, and a 3.2% equity shareholder in, InnoWell Pty; InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the AU$30 million Australian Government-funded Project Synergy. H.H. received consultancy fees from Ono Pharmaceutical and an honorarium from Xian Janssen Pharmaceutical. In the past 3 years, R.C.K. was a consultant for Cambridge Health Alliance, Canandaigua VA Medical Center, Holmusk, Partners Healthcare, RallyPoint Networks and Sage Therapeutics. He has stock options in Cerebral, Mirah, PYM, Roga Sciences and Verisense Health. L.A.M.L. reports spousal IP payments from Vanderbilt University for technology licensed to Acadia Pharmaceuticals unrelated to the present work. C.M. has served on advisory boards of Receptor Life Sciences, Otsuka Pharmaceuticals and Roche Products Limited and has received support from the National Institute on Alcohol Abuse and Alcoholism, NIMH, Department of Defense-CDMRP (US Army Research Office) DARPA, Bank of America Foundation, Brockman Foundation, Cohen Veterans Bioscience, Cohen Veterans Network, McCormick Foundation, Home Depot Foundation, New York City Council, New York State Health, Mother Cabrini Foundation, Tilray Pharmaceuticals and Ananda Scientific. P.M.P. received payment or honoraria for lectures and presentations in educational events for Sandoz, Daiichi Sankyo, Eurofarma, Abbot, Libbs, Instituto Israelita de Pesquisa e Ensino Albert Einstein, Instituto D'Or de Pesquisa e Ensino. R.P. has been paid for his editorial work on the journal *Complex Psychiatry* and received a research grant outside the scope of this study from Alkermes. J.W.S. is a member of the Scientific Advisory Board of Sensorium Therapeutics (with equity) and has received grant support from Biogen; and is the principal investigator of a collaborative study of the genetics of depression and BPD sponsored by 23andMe for which 23andMe provides analysis time as in-kind support but no payments. M.B.S. has in the past 3 years received consulting income from Acadia Pharmaceuticals, Aptinyx, atai Life Sciences, BigHealth, Biogen, Bionomics, BioXcel Therapeutics, Boehringer Ingelheim, Clexio, Eisai, EmpowerPharm, Engrail Therapeutics, Janssen, Jazz Pharmaceuticals, NeuroTrauma Sciences, PureTech Health, Sage Therapeutics, Sumitomo Pharma and Roche/Genentech; has stock options in Oxeia Biopharmaceuticals and EpiVario; has been paid for his editorial work on Depression and Anxiety (Editor-in-Chief), Biological Psychiatry (Deputy Editor) and UpToDate (Coeditor-in-Chief for Psychiatry); has also received research support from NIH, Department of Veterans Affairs and the Department of Defense; and is on the scientific advisory board for the Brain and Behavior Research Foundation and the Anxiety and Depression Association of America. In the past 3 years, D.J.S. has received consultancy honoraria from Discovery Vitality, Johnson & Johnson, Kanna, L'Oreal, Lundbeck, Orion, Sanofi, Servier, Takeda and Vistagen. M.L.K. reports unpaid membership on the Scientific Committee for the International Society for the Study of Trauma and Dissociation. The other authors declare no competing interests.

Additional information

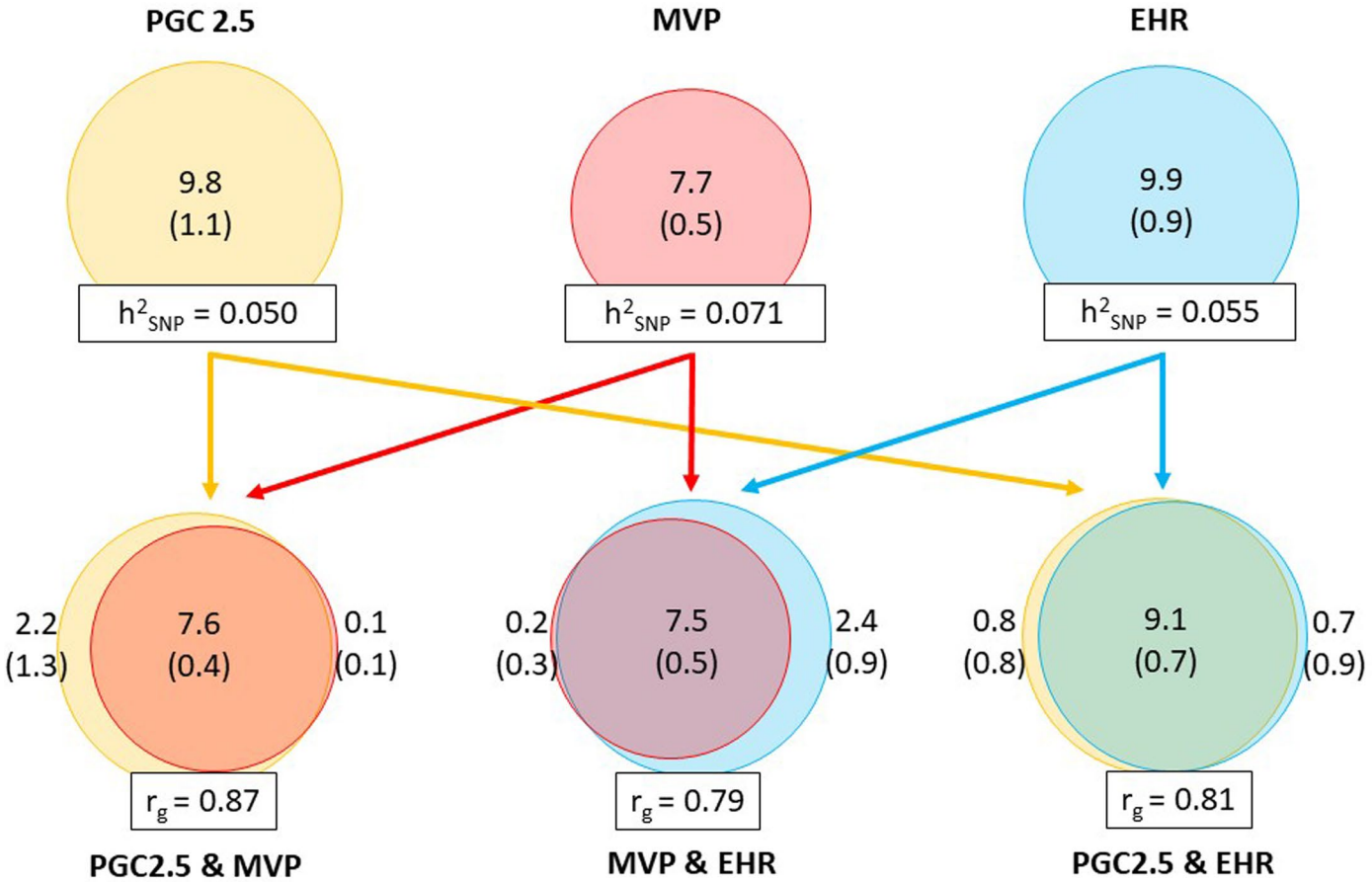
Extended data is available for this paper at https://doi.org/10.1038/s41588-024-01707-9.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41588-024-01707-9.

Correspondence and requests for materials should be addressed to Caroline M. Nievergelt.

Peer review information *Nature Genetics* thanks Jean-Baptiste Pingault and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.

https://doi.org/10.1038/s41588-024-01707-9



Extended Data Fig. 1 | Comparison of the genetic architecture of PTSD in the three main data sources. Quantification of polygenicity and polygenic overlap in the three main data subsets based on (1) symptom scores in clinical studies and cohorts assessed on a variety of instruments in Freeze 2.5 (yellow; 26,080 cases and 192,966 controls), (2) PCL (for DSM-IV) based symptom scores in the MVP (red; 32,372 cases and 154,317 controls) and (3) ICD9/10 codes in EHR studies (blue; 78,684 cases and 738,463 controls) indicate a similar genetic architecture. The circles on the top half of the plot depict univariate MiXeR estimates of the total polygenicity for each data subset. Numbers within circles indicate polygenicity values, expressed as the number of variants (in thousands, with s.e. in parenthesis) necessary to explain 90% of SNP-based heritability (h^2_{SNP}). h^2_{SNP} estimates are written in the boxes at the bottom of the circles. The Euler diagrams on the bottom half of the plot depict bivariate MiXeR estimates of the polygenic overlap between data subsets. Values in the overlapping part of the Euler diagrams denote shared polygenicity and values on the non-overlapping parts note dataset-specific polygenicity. Genetic correlations (r_g) between dataset pairs are noted in the boxes below the Euler diagrams. Arrowed lines are drawn between univariate and bivariate results to indicate which dataset pairs are being evaluated.

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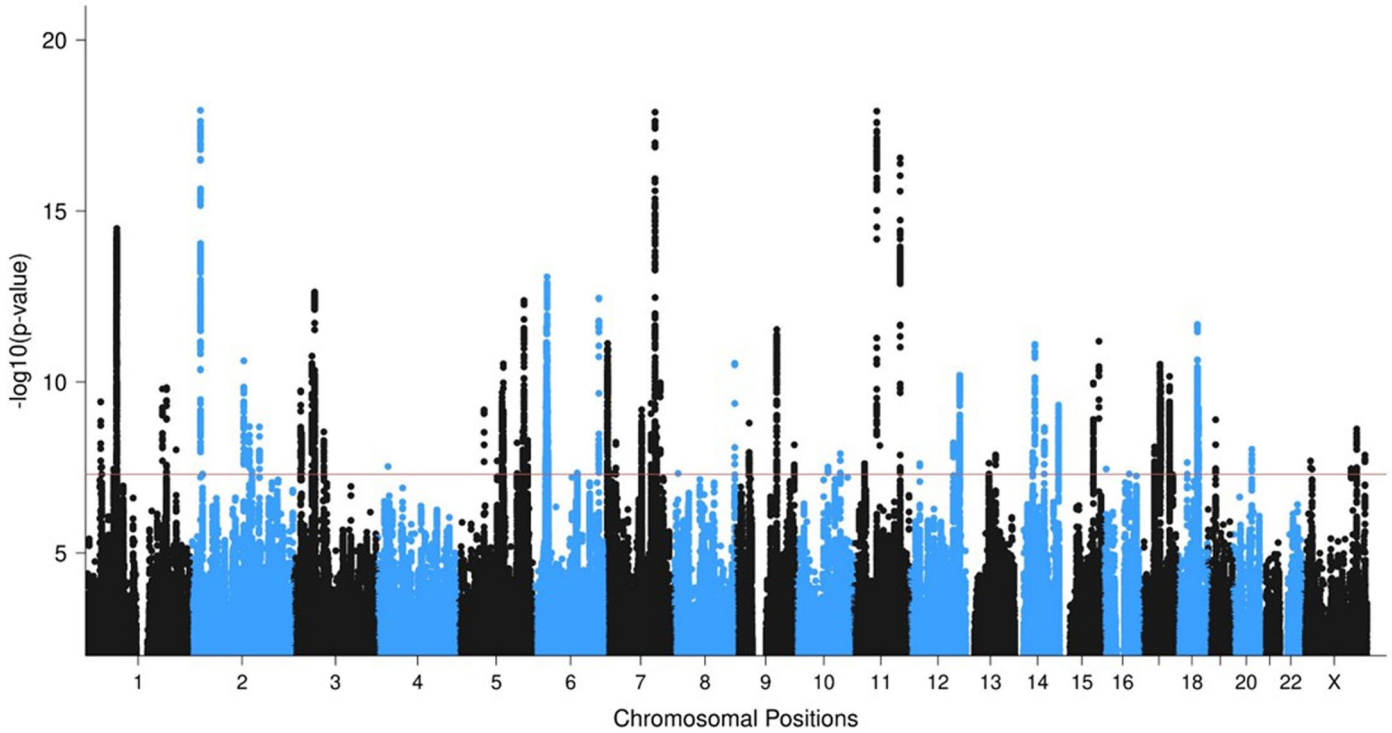

Extended Data Fig. 2 | Manhattan plot of the PTSD GWAS meta-analysis in individuals of European ancestry (EA). Results of the EA GWAS meta-analysis (137,136 PTSD cases, 1,085,746 controls) identifying 81 genome-wide significant PTSD loci. The *y*-axis refers to the $-\log_{10} P$ value from two-sided *z*-tests for effect estimates for a meta-analysis using a sample size weighted fixed-effects model. Circle colors alternate between chromosomes: even chromosomes are colored blue and odd chromosomes are colored black. The horizontal red bar indicates genome-wide significant associations ($P < 5 \times 10^{-8}$).

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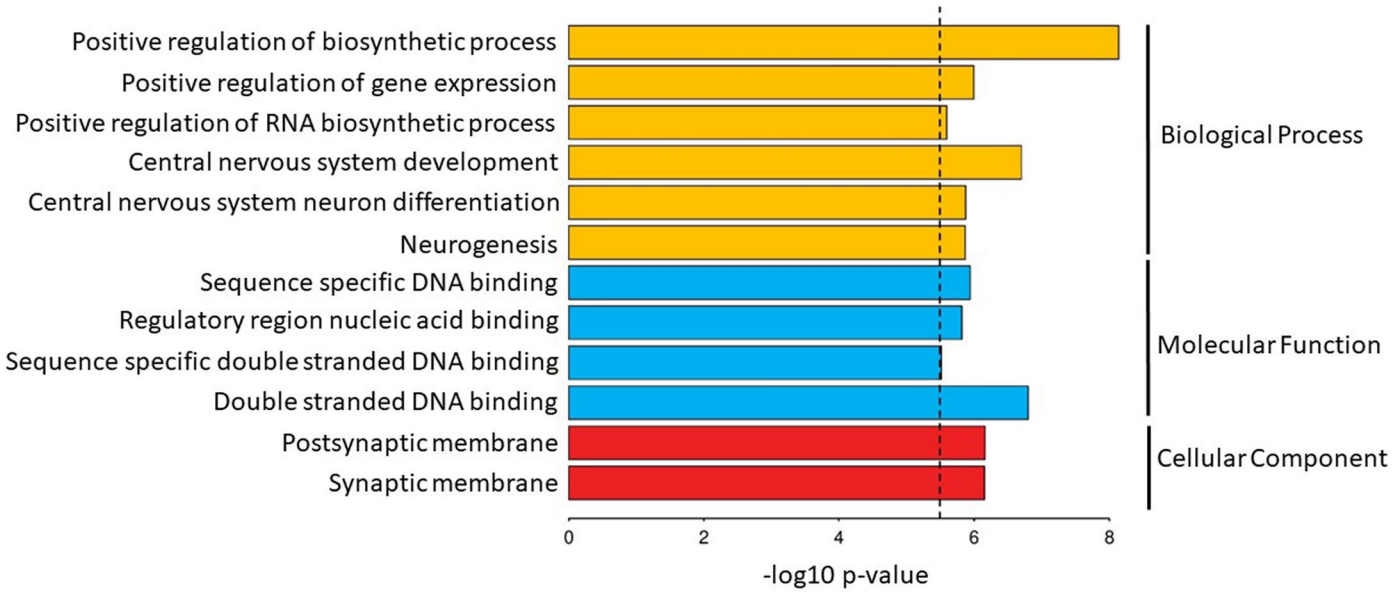

Extended Data Fig. 3 | Significant PTSD gene sets. MAGMA gene-set analysis using the Molecular Signatures Database (MSigDB) identifies 12 significant gene sets. The dotted line indicates significance adjusted for the number of comparisons ($P < 0.05/15{,}483$ gene sets). Bars depict $-\log_{10} P$ values from one-sided *t*-tests for enrichment. Corresponding gene-set names are indicated to the left of bars. Terms are clustered and colored according to their Gene Ontology term category (biological processes, yellow; molecular function, blue; cellular component, red).

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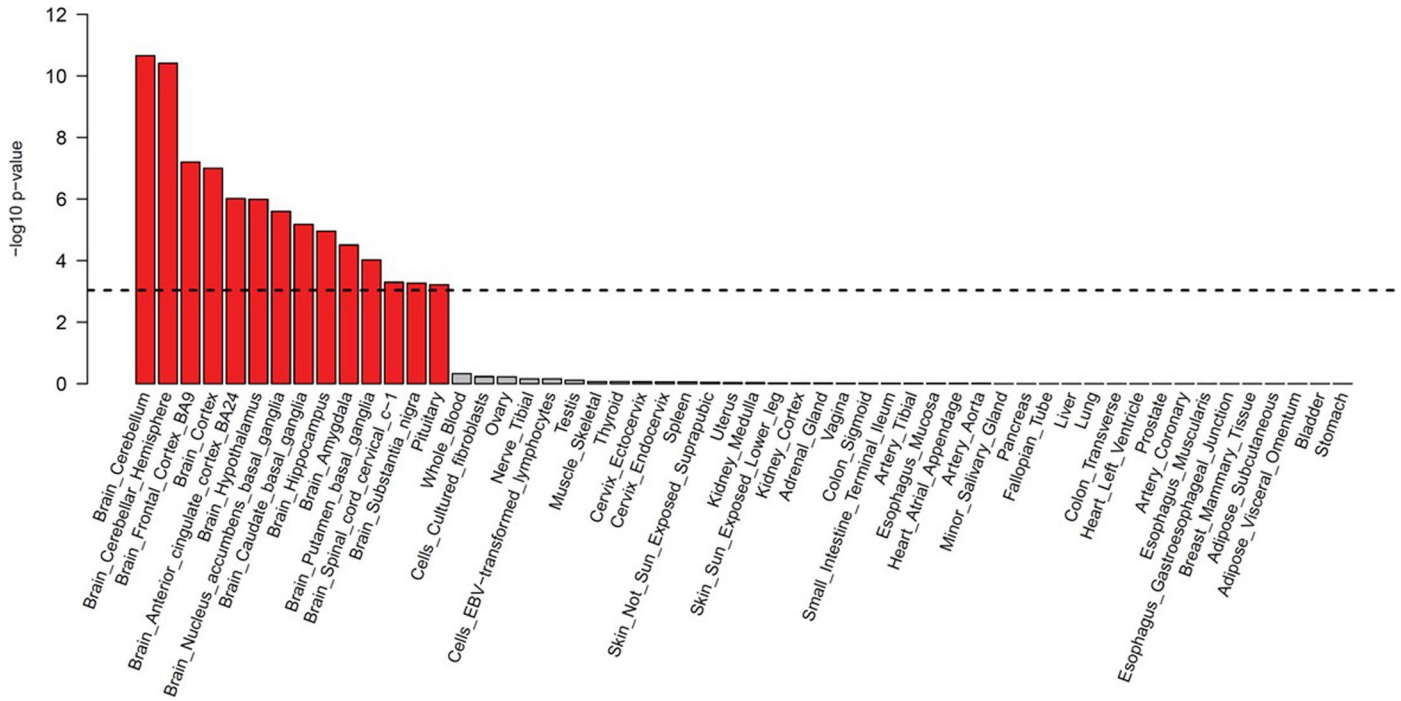

Extended Data Fig. 4 | MAGMA tissue enrichment analysis. MAGMA gene-property analysis in 53 specific tissue types from GTEx v8 shows enrichment of PTSD-related genes in 13 brain tissue types and in the pituitary. Bars depict $-\log_{10}$ *P* values from one-sided *t*-tests for enrichment. Corresponding tissue names are indicated below bars. The dotted horizontal line indicates statistical significance adjusted for the number of comparisons ($P < 0.05/53$). Significant tissues are colored red.

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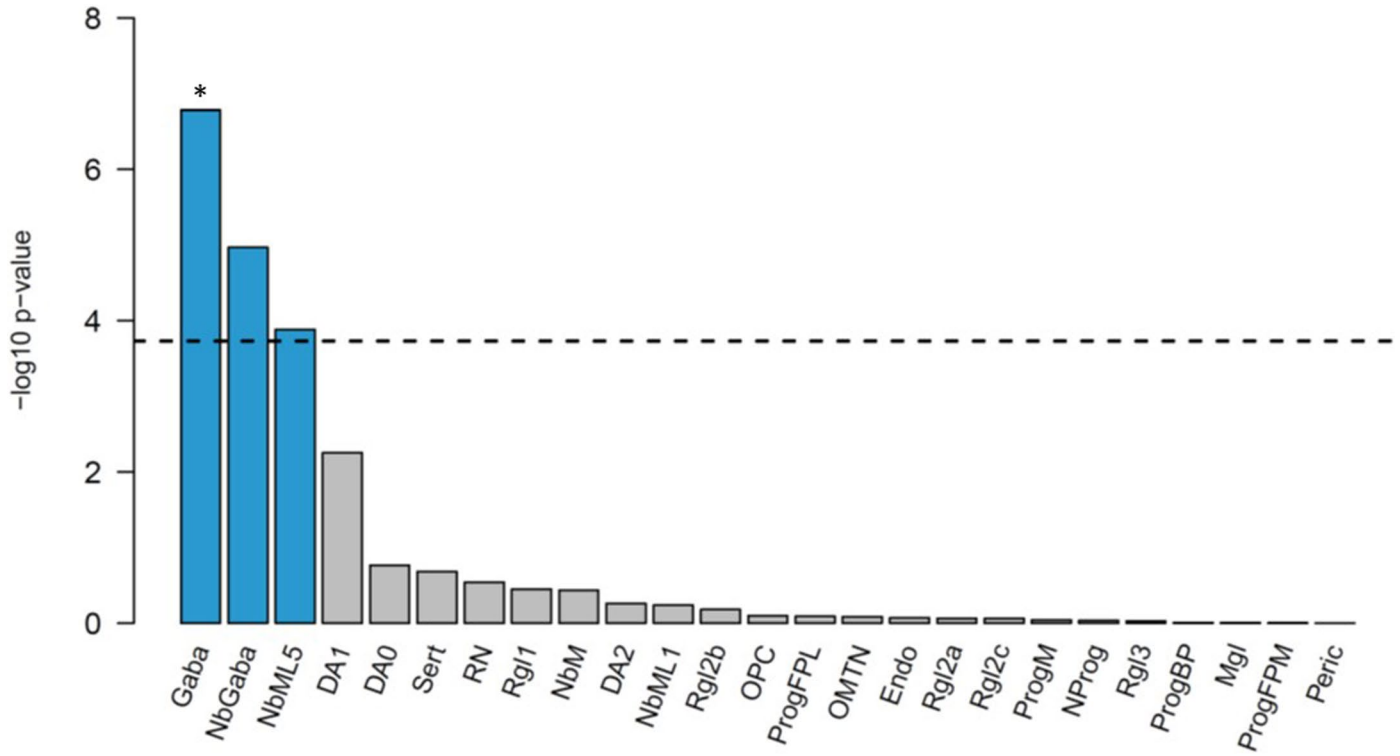
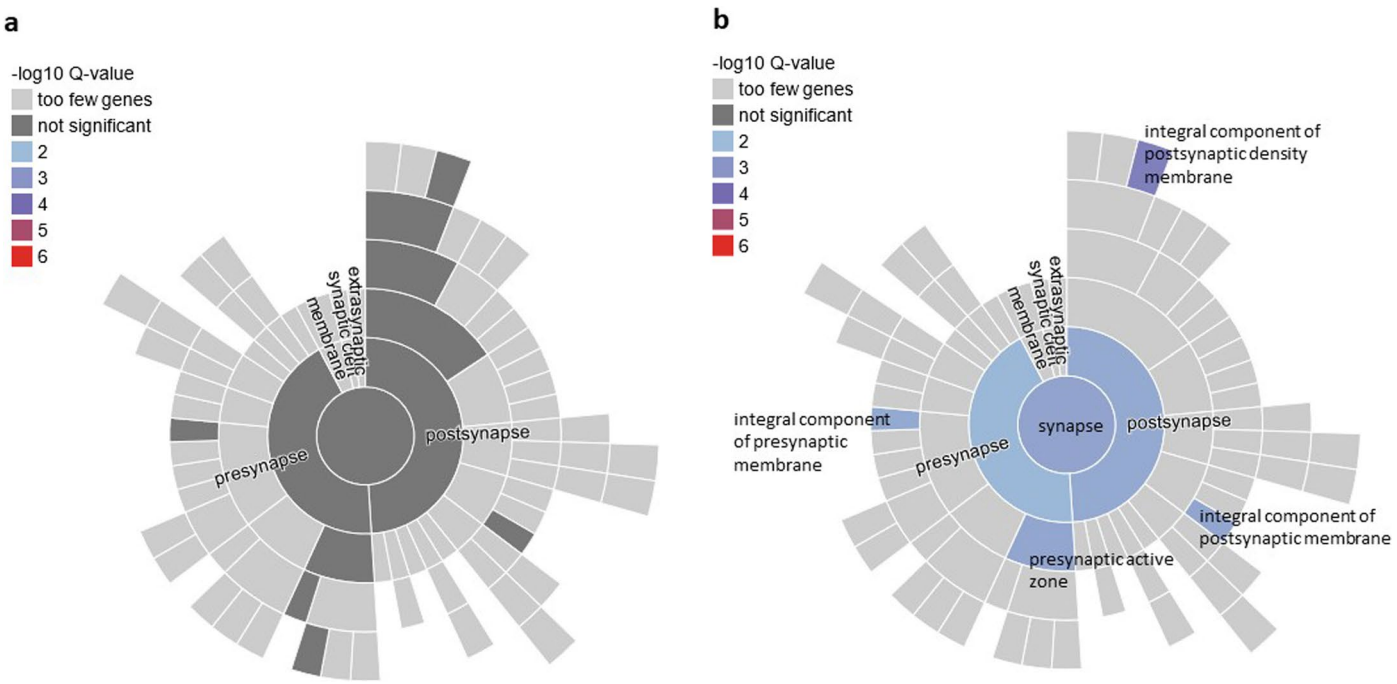


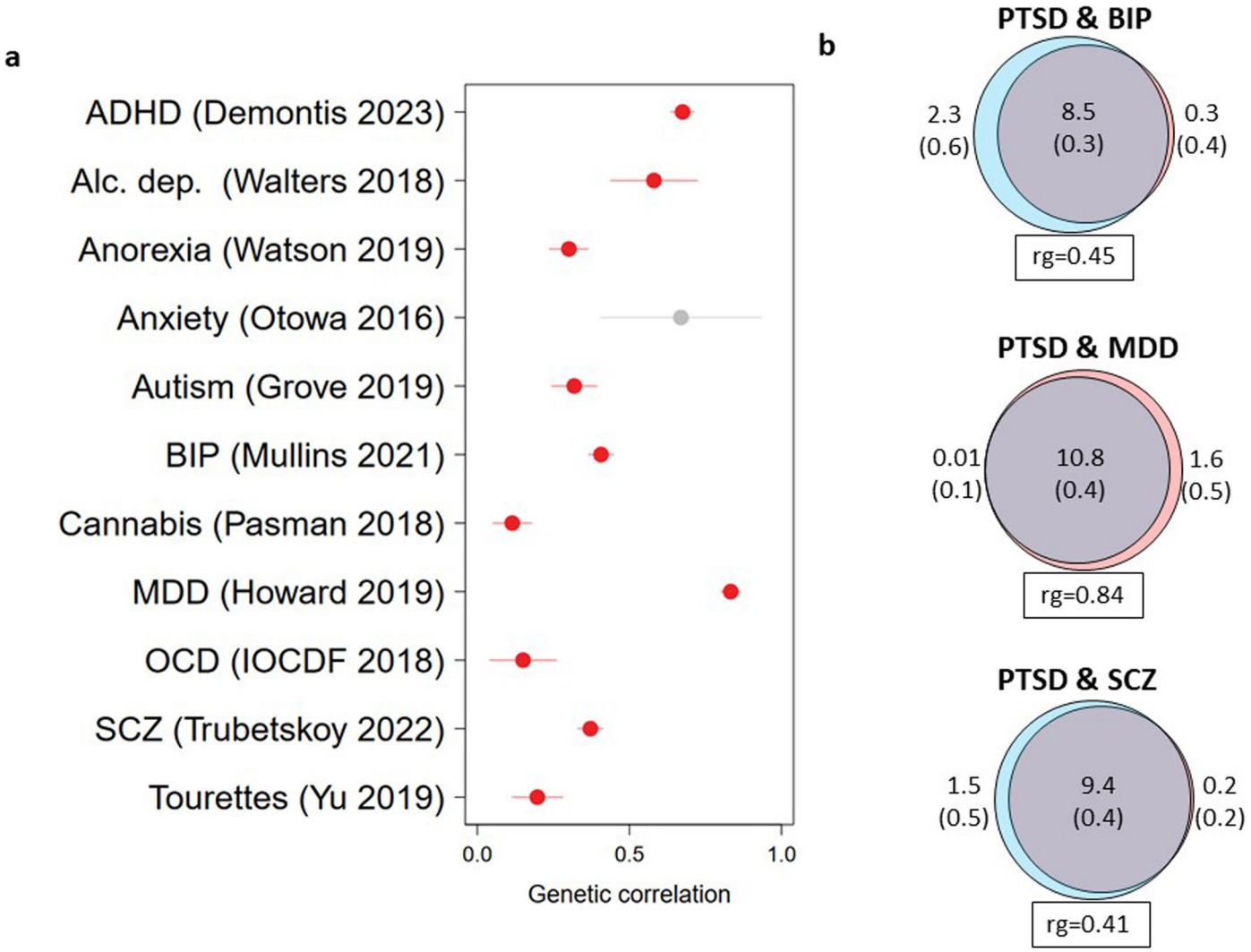
Extended Data Fig. 5 | MAGMA cell-type enrichment analysis in midbrain. MAGMA gene-property analysis of 25 midbrain cell types (GSE76381) indicates enrichment of GABAergic neurons, GABAergic neuroblasts and mediolateral neuroblasts. Vertical bars depict $-\log_{10} P$ values from one-sided *t*-tests for enrichment. Significant cell types are colored blue and gray if not. The dotted horizontal line indicates statistical significance adjusted for the number of comparisons ($P < 0.05/25$). The asterisk (*) indicates that GABAergic neurons remained significant in stepwise conditional analysis of the other significant cell types. Abbreviations: Gaba, GABAergic neurons; NbGaba, neuroblast gabaergic; NbML1-5, mediolateral neuroblasts; DA0-2, dopaminergic neurons; Sert, serotonergic neurons; RN, red nucleus; Rgl 1-3, radial glia-like cells; NbM, medial neuroblasts; OPC, oligodendrocyte precursor cells; ProgFPL, progenitor lateral floorplate; OMTN, oculomotor and trochlear nucleus; Endo, endothelial cells; ProgM, progenitor midline; NProg, neuronal progenitor; ProgBP, progenitor basal plate; Mgl, microglia; ProgFPM, progenitor medial floorplate; Peric, pericytes.

https://doi.org/10.1038/s41588-024-01707-9



Extended Data Fig. 6 | PTSD genes in SynGO. Sunburst plots show enrichment of PTSD-related genes in SynGO cellular components. The synapse is at the center ring, pre- and post-synaptic locations are at the first rings, and child terms are in subsequent outer rings. **a**, Enrichment test results for all 415 genes mapped to PTSD GWAS loci by FUMA from one of three gene-mapping strategies (positional, expression quantitative trait loci and chromatin interaction mapping). **b**, Enrichment test results for 43 genes prioritized into tier 1 using a gene prioritization strategy. Plots are colored by $-\log_{10}$ *Q*-value (see color code in the bar at left) from enrichment of PTSD genes relative to a brain-expressed background set.

https://doi.org/10.1038/s41588-024-01707-9



Extended Data Fig. 7 | Genetic correlations and polygenic overlap between PTSD and other psychiatric disorders. a, Genetic correlations (r_g) with standard error between PTSD and 11 other psychiatric disorders are indicated by circles that are drawn along the *x*-axis. Red dots indicate SNP-based heritability (h^2_{SNP}) *z*-score >6 in the psychiatric disorder GWAS and colored gray to indicate *z*-score <6 (r_g estimates may be unreliable). The first author and publication year of source summary data are noted in parenthesis following the disorder name. **b**, Quantification of the polygenic overlap between PTSD and other psychiatric disorders. Euler diagrams depict Bivariate MiXeR analysis of PTSD (blue circles) and bipolar disorder (BIP), major depression (MDD) and schizophrenia (SCZ) (red circles). Values in the overlapping part of the Euler diagrams denote shared polygenicity (expressed as the number of influential variants, in thousands, with s.e. in parenthesis), and values in the non-overlapping part indicate dataset-specific variation. r_g between dataset pairs are noted in the boxes below the Euler plots. Abbreviations: ADHD, attention deficit hyperactive disorder; Alc. dep., alcohol dependence; BIP, bipolar disorder; MDD, major depression; OCD, obsessive compulsive disorder; SCZ, schizophrenia.

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Last updated by author(s): 11/21/2023

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No specific software was used for data collection in this study.
Data analysis	For datasets processed by the PGC-PTSD analyst, quality control utilized the RICOPILI pipeline version 2019_Oct_15.001; phasing and imputation was done with Eagle v2.3.5 and minimac3, respectively, with the Haplotype Reference Consortium as a reference panel. Ancestry was inferred in the aforementioned datasets using a global reference panel (https://github.com/nievergeltlab/global_ancestry) and the SNPweights program. Studies with data sharing restrictions detail their methods in associated papers or in Supplementary Text. GWAS was performed with stratification by ancestry group and study. Strata were only analyzed if they had a minimum of 50 cases and 50 controls, or alternatively 200 subjects total. Where noted (Supplementary Table 2), small studies of similar composition were jointly genotyped so that they could be analyzed together as a single unit. For GWAS, the association between each SNP and PTSD was tested under an additive genetic model, using a regression model appropriate to the data structure. The statistical model, covariates, and analysis software used to analyze each study is detailed in Supplementary Table 28. In brief, studies of unrelated subjects with continuous (case/control) measures of PTSD were analyzed using PLINK 1.9, using a linear (logistic) regression model which included 5 PCs as covariates. For studies that retained related subjects, analyses were performed using methods that account for relatedness. QIMR was analyzed using GEMMA v0.96, including the first five PCs as covariates. RCOG was analyzed using the generalized disequilibrium test (PMID: 19732865). UKBB was analyzed using BOLT-LMM including 6 PCs, and batch and center indicator variables as covariates. VETS was analyzed using BOLT-LMM v2.3.5 including 5 PCs as covariates. EHR based studies that included related subjects were analyzed using saddle point approximation methods to account for case/control imbalances. AGDS and QIM2 were analyzed using SAIGE including 4 PCs and study specific covariates. BIOV was analyzed using SAIGE including 10 PCs and age of record. ESBB, FING, HUNT, and SWED were analyzed using SAIGE including 5 PCs. UKB2 was analyzed using REGENIE including 6 PCs, assessment center, and genotyping batch covariates. GWAS was additionally performed stratified by sex. For the X chromosome analysis, sex was added as a covariate.

Meta-analysis was conducted in METAL. Follow-up analyses were performed using LocusZoom, GCTA Conditional and Joint Analysis, LDSC, MiXeR (v1.3), LAVA, PRS-CS, FUMA v1.4.1, MAGMA v1.0.8, SUSIE, SMR software (v1.03), JEPEGMIX2-P, and SynGO.

Analysis code is made available in a public repository (https://github.com/nievergeltlab/freeze3_gwas; DOI: 10.5281/zenodo.10182702).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Summary statistics for PGC PTSD Freeze 3 will be made available upon publication under the accession ID ptsd2024 via the PGC website (https://pgc.unc.edu/for-researchers/download-results/). Access to study level summary statistics and genotype data can be applied for by using the PGC data access portal (https://pgc.unc.edu/for-researchers/data-access-committee/data-access-portal/).

Datasets used in follow-up analysis are available with associated software (LocusZoom, FUMA, MAGMA, SMR, SUSIE). Pan-UK Biobank summary statistics are available to download at https://pan.ukbb.broadinstitute.org/. Drug-class and drug-set analyses were done using the Drug Gene Interaction Database DGIdb v4.2.0 (https://www.dgidb.org/downloads), Psychoactive Drug Screening Database Ki Database (https://pdsp.unc.edu/databases/kiDownload/), ChEMBL v27 (https://chembl.gitbook.io/chembl-interface-documentation/downloads), Target Central Resource Database v6.7.0 (http://juniper.health.unm.edu/tcrd/download/), and DSigDB v1.0 (https://dsigdb.tanlab.org/DSigDBv1.0/download.html). Reference panels used are either publicly available (1000G Phase 3: https://www.internationalgenome.org/data) or upon request (Haplotype Reference Consortium: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5388176/; SISu: https://thl.fi/en/web/thl-biobank/for-researchers/sample-collections/thl-biobank-imputation-reference-panel).

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	We have performed sex-stratified analysis and measured the genetic correlation of males and females to insure no loss sex-specificity in our main analyses.
Population characteristics	Participant ages varied across cohorts, the median cohort average age of PTSD cases was 38 years old. Participants were of genetically determined European (N=1,222,882), African (N=51,034), and American (N=7,017) ancestries. Participants were genotyped on Illumina (84 studies) or Affymetrix arrays (10 studies). PTSD assessment followed clinical definitions/self-report (N=84 studies) or determination from electronic health records (N=10 studies).
Recruitment	Recruitment strategies varied by cohort, the details are in the supplementary material. Sample selection biases may have been present. For military populations, successful induction into the military may imply differences from civilian populations. Healthcare based populations may be unique in that access to medical care implies they have generally higher incomes and therefore may not represent the average person from the populations they are drawn from. These biases may generally affect external validity of results, however, we note that we have meta-analyzed a broad spectrum of populations and found that the general genetic signal we identify replicates across them.
Ethics oversight	Studies were approved by the relevant institutional review boards and the UCSD IRB (protocol #16097×).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size was not predetermined, but instead reflects our best effort to aggregate all possible studies with genome-wide genotype data and robust phenotyping of post traumatic stress disorder. This open, international collaboration supported by the Psychiatric Genomics Consortium includes contributions from 94 studies and to our knowledge represents the largest genome-wide study of PTSD to date. Based on the available data, we have made efforts to maximize the use of the genotyped samples. This includes developing the infrastructure and

	appropriate statistical modeling to include both family-based and case/control cohorts in the same genome-wide analysis, and including trans-ancestral analysis of African, European, and Latino ancestry individuals. We have also performed power analysis for the current genome-wide study. For instance, we estimate that the full discovery meta-analysis has >80% power to detect variants associated with PTSD with true odds ratios >= 1.1 and minor allele frequency > 0.2. This power and sample size are consistent with successful GWAS of many other psychiatric traits
Data exclusions	Data exclusions were performed based on (a) failure of pre-determined data quality control criteria and (b) planned phenotype exclusions to insure valid case/control criteria. For quality control, individuals were excluded if they were observed to have low genotyping quality (detailed in methods). Ancestries other than African, European, or Latino were excluded due to insufficient sample size for a meaningful analysis in the currently available data. For phenotype-based exclusions, we omit individuals lacking phenotype information for PTSD. Cohorts with other exclusion criteria as part of their original study recruitment are detailed in the Supplementary Information. The metrics used as exclusion criteria were established prior to the analyses, but some thresholds used for exclusion (e.g. cutoffs from ancestry analysis to define ancestry strata) were evaluated during the QC process. All of the above exclusions were made in accordance with the planned study protocol, and are detailed in the manuscript.
Replication	We attempted trans-ethnic replication of all genome-wide significant loci in the study. As described in the manuscript, direct replication was not found. We note that lack of replication of across ancestry groups may be due to lack of power in the replication samples or differing linkage disequilibrium patterns. For replication of a general PTSD signal in the data and to indicate generalizability of the overall results across cohorts, polygenic risk score analyses and genetic correlations were used. In all instances, polygenic risk scores derived from subsets of this study successfully predicted PTSD phenotypes in holdout data and significant genetic correlation was seen across different subsets of the data.
Randomization	Randomization of experimental groups was not applicable to this study. The experimental conditions are determined by each individual's genetics, which are fixed at conception. Conceptually this reflects a randomization of the alleles inherited from each individual's parents (i.e. mendelian randomization), but it does not involve randomization of experimental conditions by the researchers in a classical sense. Our study assess the observed association between that natural randomization of genotype and the ascertained phenotype of PTSD.
Blinding	Blinding is not relevant to the current study. Samples were not allocated to different conditions by the researches, and the phenotype ascertainment process is fully separate from the genotyping process.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging