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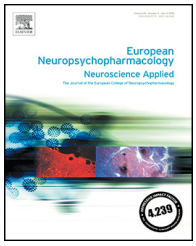

The effect of genetic vulnerability and military deployment on the development of post-traumatic stress disorder and depressive symptoms

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Abstract
Exposure to trauma strongly increases the risk to develop stress-related psychopathology, such as post-traumatic stress disorder (PTSD) or major depressive disorder (MDD). In addition, liability to develop these moderately heritable disorders is partly determined by common genetic variance, which is starting to be uncovered by genome-wide association studies (GWASs). However, it is currently unknown to what extent genetic vulnerability and trauma interact. We investigated whether genetic risk based on summary statistics of large GWASs for PTSD and MDD predisposed individuals to report an increase in MDD and PTSD symptoms in a prospective military cohort ($N = 516$) at five time points after deployment to Afghanistan: one month, six months and one, two and five years. Linear regression was used to analyze the contribution of polygenic risk scores (PRSs, at multiple p-value thresholds) and their interaction with deployment-related trauma to the development of PTSD- and depression-related symptoms. We found no main effects of PRSs nor evidence for interactions with trauma on the development of PTSD or depressive symptoms at any of the time points in the five years after military deployment. Our results based on a unique long-term follow-up of a deployed military cohort suggest limited validity of current PTSD and MDD polygenic risk scores, albeit in the presence of minimal severe psychopathology in the target cohort. Even though the predictive value of PRSs will likely benefit from larger sample sizes in discovery and target datasets, progress will probably also depend on (endo)phenotype refinement that in turn will reduce etiological heterogeneity.

1. Introduction

Deployment to a combat zone constitutes a major risk factor for the development of several debilitating psychiatric disorders such as post-traumatic stress disorder (PTSD) and major depressive disorder (MDD) (Hoge et al., 2006; Reijnen et al., 2015). Nevertheless, only a relatively small proportion of individuals develop psychopathology after traumatic experiences during deployment and the majority is resilient and remains unaffected, depending on factors such as trauma severity or the number of experienced events (Karam et al., 2014; Kessler et al., 1995; Kok et al., 2012). These different outcomes can partly be explained by common genetic variation. Compelling evidence suggests that both PTSD and MDD have a heritable component, with single-nucleotide polymorphism (SNP)-based estimates ranging from 0.07 (in males) to 0.29 (in females) (Duncan et al., 2018) and 0.09 (Wray et al., 2018), respectively. However, it is currently unknown to what extent genetic risk interacts with traumatic experiences in increasing the risk for MDD or PTSD.

Recently, large genome-wide association studies (GWASs) were published for both PTSD (Stein et al., 2016; Duncan et al., 2018) and MDD (Hyde et al., 2016; Wray et al., 2018), aiming to elucidate the role of common genetic variation in these disorders. Results from these studies provide estimates of genetic risk for these disorders and can be used to generate polygenic risk scores (PRSs) in other, independent, cohorts (Wray et al., 2014). The use of PRSs for PTSD and MDD in a large longitudinal cohort exposed to trauma may further elucidate the interaction of genetic vulnerability and trauma exposure on the development of psychopathology and could be of value to predict vulnerability.

Here, we hypothesized that genetic susceptibility for increase in self-reported PTSD- and MDD-related symptoms (as indicated by higher PRSs) in interaction with trauma exposure during military deployment determines the degree to which these symptoms become manifest in a period of up to five years after deployment. In addition, we explored relations of PRSs with symptom levels prior to deployment and the interaction of PRSs with childhood trauma on pre- and the development of post-deployment symptom levels.

2. Experimental procedures

2.1. Participants and general procedure

Participants of the present study were military deployed to Afghanistan for 4 months between 2005 and 2008, either as part of a Provincial Reconstruction Team or as part of the International Security Assistance Force (see outlined in Reijnen et al., 2015 and Van Zuiden et al., 2011). All 1032 participants gave both written and oral informed consent. Assessments and data collection took place prior to, as well as one month, six months and one, two and five years after deployment. A previous study provides general information about common duties and deployment-related potentially traumatic events (Reijnen et al., 2015). Study approval was granted by the University Medical Center Utrecht (UMCU) Institutional Review Board.

2.2. Genetic data

DNA isolated from blood of 1015 participants was genotyped on the Illumina Human OmniExpress-24 v1.1 BeadChip array (Illumina, San Diego, CA, USA). A total number of 713,040 markers was present on this chip. Data underwent extensive pre-imputation quality control (QC, see Supplementary Table S1). First, we removed subjects with a genotype call

rate < 0.95, discordant genetic and reported sex in phenotype data, excess heterozygosity rate (heterozygosity > 3SD from the mean) or excess homozygosity (heterozygosity < 3SD from the mean) and a relatedness coefficient (PI-HAT) > 0.1 (one of a pair of related individuals was removed at random). Second, we removed non-autosomal variants, SNPs with a genotype call rate < 0.95, SNPs out of Hardy-Weinberg Equilibrium (HWE test p-value $< 1 \times 10^{-6}$) and SNPs with a strand-ambiguous AT/CG genotype. Finally, as a preparatory step for imputation, we removed SNPs that were not present in the imputation reference panel or had a difference in minor allele frequency (MAF) > 0.15 compared to the reference panel. A total number of 963 individuals and 675,453 SNPs remained after pre-imputation QC.

We imputed the data on the Michigan Imputation Server (Das et al., 2016) using the Haplotype Reference Consortium Release 1.1 (McCarthy et al., 2016) as a reference panel and Eagle version 2.3 as a phasing algorithm (Loh et al., 2016). We performed post-imputation QC, where we removed SNPs that had a MAF < 0.05, imputation R^2 (INFO score) < 0.3 and MAF difference from the reference panel exceeding 0.15 (see Supplementary Table S2). After post-imputation QC, the data contained a total of 5,361,288 SNPs. We extracted genotype dosages from the imputed data for individuals with a Central European (CEU) ancestry according to the first two principal components of the genetic data using HapMap3 populations as a reference (see Supplementary Fig. S1). We only included individuals with European ancestry (constituting the vast majority of our cohort), to match the ancestry of discovery datasets used for PRS calculation and thus rule out confounding due to population stratification in our analyses.

2.3. Discovery GWAS data

We obtained summary statistics for recent GWASs of PTSD and MDD. For PTSD, this included results for three cohorts within the Army Study to Assess Risk and Resilience in Servicemembers (STARRS) (totaling 2812 cases and 6244 controls of European American Ancestry) (Stein et al., 2016) and results of the largest published PTSD GWAS (2424 cases and 7113 controls of European ancestry) (Duncan et al., 2018). For depression, we used data from the largest MDD case-control GWAS (135,458 case and 344,901 controls) (Wray et al., 2018) and a large self-report depression GWAS (75,607 cases and 231,747 controls) (Hyde et al., 2016). Although the full results from Wray et al. included the Hyde et al. cohort, the publicly available summary statistics did not include these data due to sharing limitations.

From discovery GWAS datasets, we removed all variants other than SNPs (e.g. indels), non-autosomal SNPs, SNPs with MAF < 0.05, SNPs with imputation INFO score < 0.8, strand-ambiguous A/T or C/G genotype, and duplicate or multiallelic SNPs. For the Duncan et al. PTSD GWAS, allele frequencies and imputation INFO scores were not available in summary statistics. However, SNPs with INFO scores < 0.9 were reported to be removed during QC (Duncan et al., 2018) and we filtered for SNPs with MAF ≥ 0.05 using frequencies calculated on the European subset of 1000 genomes phase 3 (Altshuler et al., 2012) as a reference.

To improve the predictive power of our PRSs, we meta-analyzed both PTSD studies and both MDD studies. First, to exclude the possibility of confounding due to sample overlap between these studies, we used disequilibrium score regression (LDSC) to calculate the bivariate intercept. In the absence of sample overlap the intercept is 0, but this value increases when shared samples are present between GWAS datasets (Bulik-Sullivan et al., 2015). In LDSC, LD scores were calculated in 1 centimorgan (cM) windows around HapMap3 SNPs using 1000 genomes phase 3 as a reference for LD (Altshuler et al., 2012, 2010). Second, we applied inverse variance-weighted fixed effects meta-analysis in METAL (Willer et al., 2010), generated quantile-quantile plots of p-value distributions for PTSD and MDD meta-analyses and calculated the genomic inflation factor (lambda). For MDD (Wray et al., 2018), association statistics for a limited set of ten thousand independent top SNPs including Hyde et al. data were publicly available. We used these data to calculate the correlation between effect sizes and association *p*-values of the original publication with those of our MDD meta-analysis (which is based on the same data). We used the meta-analyzed PTSD and MDD GWASs as discovery data for PRS calculation.

2.4. Polygenic risk score calculation

We ruled out the possibility of sample overlap between our target cohort and discovery GWAS datasets. Prior to PRS calculation, we removed linkage disequilibrium (LD) from the discovery data using a clumping procedure in PLINK version 1.90b3z (Chang et al., 2015) where all correlated SNPs in a genetic window, except the SNP with the lowest association *p*-value, were removed (first using a genetic window of 250kilobase and an LD $R^2 > 0.5$ followed by a second run using a genetic window of 5000 kb and an LD $R^2 > 0.2$). Additionally, we excluded all SNPs in genomic regions with strong or complex LD structures (e.g. the MHC region on chromosome 6) (Supplementary Table S3). We used the European subset of 1000 genomes phase 3 as a reference for LD (Abecasis et al., 2012). PTSD and MDD PRSs were calculated using the score function in PLINK for each of 13 sets of SNPs selected on different association *p*-value thresholds in the discovery GWAS (P_T): $< 5 \times 10^{-8}$, $< 5 \times 10^{-7}$, $< 5 \times 10^{-6}$, $< 5 \times 10^{-5}$, $< 5 \times 10^{-4}$, $< 5 \times 10^{-3}$, < 0.05, < 0.1, < 0.2, < 0.3, < 0.4, < 0.5 and ≤ 1). For PTSD, we were only able to calculate PRS for the latter eleven P_Ts, as an insufficient number of SNPs was available for the most stringent P_Ts.

2.5. Psychopathology outcomes

PTSD symptoms were measured prior to and one month, six months and one, two and five years after deployment, whereas for depressive symptoms all but the five year post-deployment measurement were available. PTSD and depressive symptoms were evaluated using the Self-Report Inventory for PTSD (SRIP) (Hovens et al., 2002) and the depression subscale of the symptom checklist-90 (SCL-90) (Arrindell et al., 2003), respectively. The correlation of change in depressive symptoms and PTSD symptoms was significant

from pre- to post-deployment (one month: Pearson's rho (r) = 0.11, p = 0.03; six months: r = 0.41, $p = 1.3 \times 10^{-15}$; one year: r = 0.62, $p < 2.2 \times 10^{-16}$; two years: r = 0.56, $p < 2.2 \times 10^{-16}$). A self-report checklist described in a previous study (Reijnen et al., 2015) was used to assess exposure to potentially traumatic events, including direct combat. The self-report Early Trauma Inventory was used to assess potentially traumatic events during childhood (subdivided in physical, sexual and emotional abuse; Bremner et al., 2007).

2.6. Statistical analyses

Paired two-tailed t-tests were used to compare pre- and post-deployment psychopathology symptom levels. We first analyzed the association between PRSs and childhood- and deployment trauma (e.g. *trauma during deployment* ~*PRS PTSD* $_{PT\ 0.0.5}$) using a multiple-testing corrected significance threshold for two measurements and two models tested ($p < 0.05/4 = 0.0125$).

For primary analyses, linear regression models were used with post-deployment PTSD symptom levels as the dependent variable and as indicators: pre-deployment PTSD symptom levels, a PRS for PTSD (11 different P_T, see above), trauma during deployment, childhood trauma, sex, age, and the five first principal components (adjusting for ethnicity) (e.g. *PTSD symptoms* $_{post\_six\_months}$ ~*PTSD symptoms* $_{pre}$ + *PRS PTSD* $_{PT\ \ 0.05}$ + trauma *during deployment* + *childhood trauma* + *sex* + *age* + *PC1* + *PC2* + *PC3* + *PC4* + *PC5*). Subsequently, the interaction of the PTSD PRSs with trauma exposure during deployment was added to the model, in a model including all PRS x covariate and trauma exposure x covariate interactions to correct for possible confounding (Keller, 2014). Identical models were used for depressive symptoms and MDD PRSs (13 P_T).

In secondary analyses, we examined the association of PRSs with pre-deployment psychopathology levels and the interaction of PRSs and childhood trauma on pre- and the development of post-deployment psychopathology levels. Homogeneity of variance, absence of outliers (Cook's Distance < 1) and normal distribution of the residuals were confirmed by inspecting plots of the main models. To correct for multiple testing in primary and secondary analyses, the significance threshold was set at 0.05/18 = 0.0028 to adjust for analyses of five time points for PTSD symptoms and four for depressive symptoms using two models (one with only main and one including interaction).

3. Results

3.1. Descriptive statistics

Table 1 lists sample characteristics, including age, sex, number of traumatic events during military deployment and childhood, number of previous deployments, and pre- and post-deployment levels of PTSD and depressive symptoms. PTSD symptoms were significantly higher one ($p < 0.001$) and six (p = 0.03) months and five years (p = 0.002) after deployment compared to pre-deployment, but not one (p = 0.95) and two (p = 0.21) years after deployment. In contrast, depressive symptoms were significantly higher one (p = 0.008) and two years (p = 0.0001) post-deployment, whereas one month (p = 0.13) and six months (p = 0.07) post-deployment no significant increases were present compared to pre-deployment depressive symptoms (see Table 1).

3.2. Meta-analyses of discovery datasets and PRS calculation

Bivariate LDSC of PTSD summary statistics and MDD GWAS results did not reveal any intercepts more than standard error above 0, indicating no suspected presence of sample overlap. Genetic correlation calculated with LDSC between MDD datasets was high (r_g = 0.86, se = 0.03) which is as expected for GWASs of the same phenotype (see Supplementary Table S4). Reliable genetic correlation estimates between PTSD datasets could not be calculated due to low sample size. Inflation of test statistics was absent in the meta-analysis of PTSD GWAS results (5236 cases; 13,357 controls, λ_{GC} = 1.011; λ_{GC1000} = 1.001) while high inflation was observed in the MDD meta-analysis (135,458 cases; 344,901 controls; λ_{GC} = 1.44; λ_{GC1000} = 1.002) as reported in the original manuscript (Wray et al., 2018). We found high correlations between effect estimates (R^2 = 0.997) and association p-values (R^2 = 0.97) of our meta-analysis and the original result for 8398 SNPs for which full results were publicly available. PRSs for PTSD and MDD were calculated using meta-analysis results (PRS distributions per P_T are shown in Supplementary Figs. S3 and S4).

3.3. Trauma during deployment and childhood trauma

Childhood trauma was significantly associated with PTSD PRSs at $P_T < 0.2$ (beta = 0.02, p = 0.007) after correction for multiple testing, while nominal significant associations were observed at $P_T < 0.1$ (beta = 0.02; p = 0.02) and < 0.3 (beta = 0.02, p = 0.02), and at $P_T < 0.1$ for MDD PRSs (beta = 0.09; p = 0.02). Trauma during deployment was only associated at nominal significance with MDD PRSs at $P_T < 5 \times 10^{-5}$ (beta = −0.49, p = 0.02).

3.4. PTSD symptoms

The development of post-deployment PTSD symptoms at any time point (one month, six months and one, two and five years) was not associated with PTSD PRSs at any P_T. In addition, there were no significant interaction effects of PTSD PRSs with trauma during deployment on the development of PTSD symptoms after deployment (see Table 2, all p-values > 0.02). The added explained variance of PTSD PRSs in the main models was very low or absent (e.g. P_T 0.05 included as main effect, with PTSD symptoms six months post-deployment as the dependent variable: R^2 = 0.2779; P_T 0.05 excluded from the model: R^2 = 0.2772).

In secondary analyses, PTSD PRSs were not associated with pre-deployment PTSD symptoms (neither direct nor in

Table 1 Sample characteristics (total $N = 516$).

Age (mean, SD)	29.5 (9.3)				
Sex (% male)	91.5				
Number of deployment-related trauma events (mean, SD)	4.6 (3.2)				
Number of early trauma events (mean, SD)	3.3 (3.0)				
Number of previous deployments (mean, SD)	0.9 (1.2)				
	Pre-deployment	*One month post-deployment*	*t*	*p*	*n*
PTSD symptoms (SRIP) (mean, SD)	26.8 (4.9)	27.7 (5.9)	−3.71	*<0.001*	421
Depressive symptoms (SCL-90 depression subscale) (mean, SD)	17.9 (3.0)	18.1 (3.7)	−1.50	0.13	486
	Pre-deployment	*Six months post-deployment*	*t*	*p*	*n*
PTSD symptoms (SRIP) (mean, SD)	26.7 (4.8)	27.4 (6.8)	−2.22	*0.03*	372
Depressive symptoms (SCL-90 depression subscale) (mean, SD)	17.9 (3.0)	18.2 (4.0)	−1.80	0.07	425
	Pre-deployment	*One year post-deployment*	*t*	*p*	*n*
PTSD symptoms (SRIP) (mean, SD)	26.8 (5.1)	26.8 (6.8)	−0.06	0.95	296
Depressive symptoms (SCL-90 depression subscale) (mean, SD)	18.2 (3.4)	19.0 (5.6)	*−2.67*	*0.008*	*342*
	Pre-deployment	*Two years post-deployment*	*t*	*p*	*n*
PTSD symptoms (SRIP) (mean, SD)	26.7 (5.1)	26.3 (5.6)	1.24	0.21	266
Depressive symptoms (SCL-90 depression subscale) (mean, SD)	17.8 (2.8)	19.0 (5.4)	*−3.91*	*0.0001*	*328*
	Pre-deployment	*Five years post-deployment*	*t*	*p*	*n*
PTSD symptoms (SRIP) (mean, SD)	26.9 (5.2)	28.1 (7.2)	*−3.07*	*0.002*	*290*

interaction with childhood trauma; see Supplementary Table S5, all p-values > 0.02). In addition, there were no significant interactions of PTSD PRSs with childhood trauma on the development of post-deployment PTSD symptoms at any post-deployment time point (see Supplementary Table S6, all p-values > 0.01).

3.5. Depressive symptoms

No significant main or interaction effects with deployment-related trauma were observed for the MDD PRSs at any P_T on the development of depressive symptoms at any time point after deployment (see Table 3, all p-values > 0.03). Similar to PTSD, MDD PRSs added minimally or not at all to the explained variance of the main models (e.g. P_T 0.05 included as main effect, with depressive symptoms six months post-deployment as the dependent variable: $R^2 = 0.2771843$; P_T 0.05 excluded from the model: $R^2 = 0.2771822$).

In secondary analyses, PRSs for MDD were not associated with baseline depressive symptoms (neither main nor in interaction with childhood trauma; see Supplementary Table S5, all p-values > 0.04). Furthermore, there were no interaction effects of MDD PRSs and childhood trauma on the development of post-deployment depressive symptoms at any time point (see Supplementary Table S7, all p-values > 0.01).

4. Discussion

In a large prospective military cohort, we calculated PRSs derived from recent GWASs on PTSD and MDD to investigate both main effects of genetic vulnerability and the interaction with deployment-related trauma on the development of self-reported PTSD- and depression-related symptoms at five time points over five years after deployment to Afghanistan. Meta-analysis of GWAS results for two

Table 2 PTSD PRSs at all significance thresholds (P_T) in relation to the development of PTSD symptoms after deployment.

P_T PRSs	Total SNPs PTSD	One month post-deployment ($N = 421$)				Six months post-deployment ($N = 372$)				One year post-deployment (N = 296)				Two years post-deployment (N = 266)				Five years post-deployment (N = 290)			
		Main effect		PRS × deployment trauma		Main effect		PRS × deployment trauma		Main effect		PRS × deployment trauma		Main effect		PRS × deployment trauma		Main effect		PRS × deployment trauma	
		p	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*
$<5 \times 10^{-6}$	6	0.52	0.6269	0.10	0.5823	0.72	0.4606	0.97	0.0195	0.44	−1.1080	0.42	−0.4566	0.48	−0.8868	0.81	−0.1215	0.23	−1.9048	0.45	0.4670
$<5 \times 10^{-5}$	59	1.00	−0.0012	0.57	0.0751	0.45	−0.3871	0.70	−0.0658	0.07	−1.1109	*0.02*	*−0.4727*	0.43	−0.4147	0.86	−0.0332	0.43	0.5115	0.38	0.1957
$<5 \times 10^{-4}$	476	0.89	−0.0190	0.67	0.0190	0.84	0.0366	0.71	−0.0223	0.96	−0.0110	0.54	0.0417	0.99	0.0029	0.42	0.0473	0.16	0.3071	0.07	0.1225
$<5 \times 10^{-3}$	3523	0.88	0.0083	0.48	0.0137	0.96	−0.0037	0.83	−0.0054	0.93	−0.0069	0.26	−0.0341	0.88	0.0110	0.50	0.0197	0.62	0.0452	0.98	0.0008
<0.05	25,514	0.57	0.0141	0.06	0.0151	0.56	−0.0185	0.75	0.0034	0.90	−0.0046	0.47	−0.0086	0.97	−0.0012	0.14	0.0166	0.10	0.0658	0.62	0.0063
<0.1	44,633	0.84	0.0039	0.20	0.0081	0.79	−0.0067	0.69	0.0034	0.88	0.0045	0.57	−0.0055	0.96	0.0012	0.07	0.0165	0.11	0.0501	0.51	0.0065
<0.2	76,374	0.82	0.0040	0.19	0.0074	0.51	−0.0146	0.62	0.0036	0.98	−0.0005	0.53	−0.0055	0.81	0.0055	0.08	0.0139	0.09	0.0456	0.61	0.0045
<0.3	102,562	1.00	−0.0001	0.07	0.0095	0.43	−0.0159	0.33	0.0066	0.83	−0.0048	0.64	−0.0037	0.93	0.0019	0.06	0.0138	0.19	0.0322	0.50	0.0056
<0.4	125,214	0.98	0.0004	*0.04*	*0.0101*	0.62	−0.0093	0.26	0.0073	0.98	−0.0007	0.95	−0.0005	0.92	0.0020	0.11	0.0112	0.18	0.0318	0.44	0.0062
<0.5	143,907	0.89	0.0019	*0.04*	*0.0101*	0.63	−0.0090	0.27	0.0070	1.00	0.0000	0.87	−0.0013	0.93	−0.0017	0.11	0.0109	0.20	0.0299	0.52	0.0050
<1	197,108	0.84	0.0029	0.05	0.0094	0.68	−0.0075	0.28	0.0068	0.93	−0.0019	0.89	−0.0010	0.94	−0.0013	0.08	0.0119	0.19	0.0299	0.55	0.0046

Table 3 MDD PRSs at all significance thresholds (P_T) in relation to the development of depressive symptoms after deployment.

P_T PRSs	Total SNPs MDD	One month post-deployment ($N = 486$)				Six months post-deployment ($N = 425$)				One year post-deployment (N = 342)				Two years post-deployment (N = 328)			
		Main effect		PRS × deployment trauma		Main effect		PRS × deployment trauma		Main effect		PRS × deployment trauma		Main effect		PRS × deployment trauma	
		p	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β
$<5 \times 10^{-8}$	45	0.60	−0.4759	0.84	−0.0654	0.07	−2.0219	0.73	−0.1498	*0.03*	*−4.4056*	0.94	0.0526	0.51	−1.2604	0.74	0.2433
$<5 \times 10^{-7}$	101	0.25	−0.7089	0.29	−0.2528	0.09	−1.2704	0.41	−0.2448	0.45	−1.0084	0.70	−0.1939	0.57	0.7410	0.74	0.1658
$<5 \times 10^{-6}$	198	0.10	−0.7650	0.31	−0.1638	0.11	−0.9132	0.87	−0.0338	0.82	0.2321	0.73	−0.1236	0.90	−0.1223	0.94	−0.0273
$<5 \times 10^{-5}$	552	0.95	0.0189	0.92	−0.0104	0.93	−0.0311	0.71	−0.0507	0.11	1.0872	0.22	−0.3087	0.22	0.7902	0.38	−0.2171
$<5 \times 10^{-4}$	1821	0.38	−0.1577	0.83	−0.0135	0.42	−0.1752	0.49	−0.0565	0.99	0.0028	0.24	−0.1732	0.59	0.2087	0.42	−0.1175
$<5 \times 10^{-3}$	7221	0.40	−0.0872	0.34	−0.0337	0.53	−0.0810	0.52	−0.0286	0.30	−0.2303	0.09	−0.1377	0.78	0.0600	0.98	0.0018
<0.05	31,728	0.33	−0.0531	0.72	−0.0068	0.85	−0.0125	0.94	−0.0017	0.69	0.0505	0.38	−0.0418	0.61	0.0596	0.82	−0.0100
<0.1	49,995	0.16	−0.0660	0.66	−0.0071	0.73	−0.0203	0.87	0.0035	0.94	0.0074	0.33	−0.0396	0.60	0.0529	0.83	−0.0081
<0.2	78,345	0.11	−0.0636	0.55	−0.0086	0.59	−0.0267	0.84	0.0037	0.97	0.0035	0.13	−0.0528	0.44	0.0660	0.79	−0.0088
<0.3	100,527	0.11	−0.0590	0.68	−0.0055	0.67	−0.0195	0.70	0.0065	0.77	0.0250	0.18	−0.0434	0.43	0.0634	0.88	−0.0047
<0.4	118,804	0.19	−0.0481	0.97	−0.0005	0.79	−0.0118	0.52	0.0106	0.88	0.0122	0.17	−0.0435	0.51	0.0518	0.94	0.0023
<0.5	133,783	0.19	−0.0474	0.92	−0.0013	0.94	−0.0033	0.56	0.0094	0.83	0.0180	0.22	−0.0384	0.62	0.0385	0.95	0.0020
All	176,024	0.20	−0.0452	0.94	−0.0009	0.92	−0.0044	0.59	0.0086	0.92	0.0086	0.23	−0.0369	0.74	0.0248	0.99	−0.0005

PTSD studies and two MDD studies allowed us to achieve substantial power for PRS calculation. In secondary analyses, we examined the association of these PRSs with baseline depressive and PTSD symptoms and their interaction with childhood trauma. We did not find significant main or interaction effects of PRSs on PTSD or depressive symptoms at any time point after deployment. In addition, there were no significant associations with baseline symptom levels and no interactions with childhood trauma on pre- and the development of post-deployment symptoms levels.

The absence of evidence of a relation between PTSD PRSs and our outcomes may have several explanations. First, the SNP-based heritability in the European descent subsamples of the original studies was either not significant (Stein et al., 2016) or only significant in females (Duncan et al., 2018) while our target cohort largely consisted of males, thus indicating that our PRSs may have been insufficiently refined to discover significant associations. Second, the discovery GWASs (Duncan et al., 2018; Stein et al., 2016) contained mostly trauma-exposed controls, thereby excluding genetic variation associated with liability to exposure to trauma. Exposure to trauma is itself moderately heritable (True et al., 1993), which is possibly mediated by specific personality traits (e.g. harm avoidance and/or novelty seeking). As such, the PTSD PRSs do not capture much of the genetic variation associated with PTSD through specific personality traits, whereas our military cohort was not selected on these traits. This may have contributed to a difference in genetic background of PTSD in the discovery samples (Duncan et al., 2018; Stein et al., 2016) compared with our target sample. Nonetheless, the association of PTSD PRSs with childhood trauma at one P_T suggests that at least some of the genetic risk captured by the PRSs could reflect personality traits leading to more trauma exposure. Lastly, PTSD in part of the discovery sample had been caused by pre-deployment or non-military traumatic events (Duncan et al., 2018; Stein et al., 2016). In the STARRS cohort, only 24% of the soldiers had been deployed and most participants were in the age range of 18–20 years (Stein et al., 2016). Of note, PTSD caused by childhood trauma may have a different genetic etiology than PTSD caused by deployment-related trauma.

The lack of significant findings with MDD PRSs is noteworthy given the results of two previous studies confirming the validity of an MDD PRS based on a maximum of 9240 cases and 9519 controls (Ripke et al., 2013) in two different populations (Musliner et al., 2015; Peyrot et al., 2014). Peyrot et al. (2014) found both main and interaction effects of the MDD PRS and childhood trauma on risk for MDD in a study sample of 1645 patients with MDD and 340 controls. In addition, Musliner et al. (2015) found a main effect of the MDD PRS and stressful life events on depressive symptoms in a population of 8761 mainly older adults. The MDD PRSs in the present study were based on over 135,000 cases and 344,000 controls. This would expectedly lead to more valid PRSs than the ones based on the previous, much smaller GWAS (Ripke et al., 2013), even though depressive symptoms in part of the discovery data (Hyde et al., 2016) were ascertained using self-report. In contrast to PTSD, where male SNP based heritability was low and non-significant, the SNP-based heritability in the MDD GWAS (Wray et al., 2018) was significant and estimated at 8.7%. Possibly, the null finding in the present study, with very low or no added explained variances of the PRSs in our main models, was due to etiological differences in depressive phenotypes of the military cohort after deployment versus patients with a depressive episode in the general population, the minor increase in depressive symptoms between the pre-deployment and post-deployment measurements and the relatively low level of severe depression in our study sample. More specific phenotyping of heterogeneous disorders such as MDD and PTSD in both the discovery and target cohorts may be effective in this regard, as some studies have shown that this increases power to find genome-wide significant associations (CONVERGE consortium, 2015; Milaneschi et al., 2016). Furthermore, genetic correlation estimates could provide insight into genetic heterogeneity between discovery and target datasets when sample sizes are sufficient and future methodological studies could focus on loss of power in PRS analysis due to phenotypic and etiological heterogeneity.

The longitudinal design around military deployment, with psychopathology outcomes at six time points and quantification of deployment-related trauma, is the main strength of this study. The relatively healthy population represents this study's most important limitation. The increase in PTSD and depressive symptoms after deployment was small and at some time points non-significant, probably hampering the power in our analyses even with large discovery GWASs on which PRSs were calculated. Moreover, mean pre- and post-deployment scores do not fall in the range of severe psychopathology for PTSD (SRIP $\geq$ 38) (Van Zelst et al., 2003) and above-average depression. Furthermore, self-report questionnaires were used to evaluate symptom severity, which may have led to some social desirability bias. Moreover, trauma exposure questionnaires did not take subjective experience of these events into account, while this subjective experience is probably more important than the actual event (Conway et al., 2012). In addition, the present sample size may have been insufficient. This issue, however, is partly compensated for by the longitudinal design. Lastly, as mentioned above, the PRSs of PTSD were based on a relatively small GWAS (as compared to the MDD discovery dataset), compromising their validity.

Future studies may further shed light upon the validity of MDD PRSs in non-clinical and clinical samples. For PTSD, a larger upcoming GWAS by the Psychiatric Genomics Consortium (PGC) (Nievergelt et al., 2018) may yield more refined PTSD PRSs than the ones used here. In addition to increasing sample sizes, the focus in GWASs may need to be shifted towards more specific (Milaneschi et al., 2016) and/or more severe (CONVERGE consortium, 2015) phenotypes. As such, PRSs may be most informative about etiology and may ultimately be useful for prediction purposes (Smoller, 2016).

In conclusion, we used polygenic risk scores derived from large GWASs for PTSD and MDD to investigate the interaction of genetic vulnerability with potentially traumatic events on the development of these disorders in a prospective military cohort deployed to a combat zone. Our results indicate the limited validity of PTSD and MDD PRSs in this relatively healthy military population and highlight the importance of etiological heterogeneity of these disorders. Future studies investigating common genetic risk for PTSD will benefit from increased sample sizes in GWASs, but for both MDD and

PTSD phenotype refinement may be of crucial importance for progress in this field.

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Conflicts of interest

Funders had no role in design and reporting of the study. All authors reported no biomedical financial interests or potential conflicts of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2018.12.009.

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