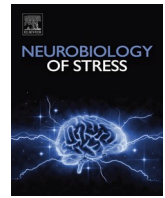


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## Neurobiology of Stress

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## Polygenic scores for empathy associate with posttraumatic stress severity in response to certain traumatic events

Frank R. Wendt<sup>a,b,\*</sup>, Varun Warriar<sup>c,2</sup>, Gita A. Pathak<sup>a,b</sup>, Karestan C. Koenen<sup>d,e,f</sup>, Murray B. Stein<sup>g,h,i</sup>, John H. Krystal<sup>a,j</sup>, Robert H. Pietrzak<sup>a,j,k</sup>, Joel Gelernter<sup>a,b,l,m</sup>, Elizabeth V. Goldfarb<sup>a,n,o</sup>, Simon Baron-Cohen<sup>c,1</sup>, Renato Polimanti<sup>a,b,1</sup>

<sup>a</sup> Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA

<sup>b</sup> VA CT Healthcare System, West Haven, CT, USA

<sup>c</sup> Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridge, UK

<sup>d</sup> Broad Institute of MIT and Harvard, Stanley Center for Psychiatry Research, Cambridge, MA, USA

<sup>e</sup> Massachusetts General Hospital, Psychiatry and Neurodevelopmental Genetics Unit (PNGU), Boston, MA, USA

<sup>f</sup> Harvard School of Public Health, Department of Epidemiology, Boston, MA, USA

<sup>g</sup> Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

<sup>h</sup> Veterans Affairs San Diego Healthcare System, San Diego, CA, USA

<sup>i</sup> Herbert Wertheim School of Public Health and Human Longevity Science, University of California San Diego, La Jolla, CA, USA

<sup>j</sup> National Center for PTSD, VA Connecticut Healthcare System, West Haven, CT, USA

<sup>k</sup> Department of Social and Behavioral Sciences, Yale School of Public Health, New Haven, CT, USA

<sup>l</sup> Department of Genetics, Yale School of Medicine, New Haven, CT, USA

<sup>m</sup> Department of Neuroscience, Yale School of Medicine, New Haven, CT, USA

<sup>n</sup> Yale Stress Center, Yale University School of Medicine, New Haven, CT, USA

<sup>o</sup> Department of Psychology, Yale School of Medicine, New Haven, CT, USA

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## ABSTRACT

**Background:** Posttraumatic stress disorder (PTSD) is triggered by environmental stressors. Empathy may predispose an individual to respond to life events differently if high empathizers are emotionally more sensitive to trauma. For the first time, we test this hypothesis using genetic information.

**Methods:** We applied polygenic scoring (PGS) to investigate the shared genetics linking empathy (measured using the Empathy Quotient (EQ), a self-report measure of empathy;  $N = 46,861$ ) and PTSD symptom severity (measured using the 6-item PTSD Checklist 6-item (PCL-6)) in the UK Biobank ( $N = 126,219$ ). Follow-up analyses were performed in the context of (1) experiencing any of 16 potential traumas, (2) the total number of traumas endorsed, and (3) the context of trauma. Autism, depression, generalized anxiety, and PCL-17 PGS were included as covariates to verify the specificity of the effect.

**Results:**  $EQ_{PGS}$  associated with PCL-6 ( $R^2 = 0.012\%$ ,  $P = 9.35 \times 10^{-5}$ ). This effect remained significant after accounting for autism, depression, PTSD, and anxiety PGS but was observed only in those who endorsed experiencing at least one traumatic event.  $EQ_{PGS}$  showed the strongest effect on PCL-6 ( $\beta = 2.32$ ,  $s.e. = 0.762$ ,  $P = 0.002$ ) among those who endorsed childhood neglect/abuse (*felt hated as a child*). With respect to case status, the highest probability of PTSD was 17.93% and 10.04% for those who endorsed “*feeling hated as a child*” and those who did not, respectively ( $P_{diff} = 0.011$ ; Cohen’s  $d = 1.951$ , 95%CI 1.70–2.20).

**Conclusions:** A genetic predisposition to higher empathy, which may index greater emotional sensitivity, predisposes an individual to more severe PTSD symptoms, especially after early-life adversity.

\* Corresponding author. Department of Psychiatry, Yale University School of Medicine, VA CT 116A2, 950 Campbell Avenue, West Haven, CT, 06516, USA.

E-mail address: [frank.wendt@yale.edu](mailto:frank.wendt@yale.edu) (F.R. Wendt).

<sup>1</sup> Joint senior authors.

<sup>2</sup> Joint first authors.

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1. Introduction

The lifetime prevalence of posttraumatic stress disorder (PTSD) is 4–7% (Goldstein et al., 2016). PTSD is unique among psychiatric disorders in that an environmental exposure, often termed an “index trauma,” is a core criterion for diagnosis. Genome-wide association studies (GWAS) have detected a common variant heritable component for PTSD of between 5 and 20% (Nievergelt et al., 2019; Stein et al., 2021) but we do not yet understand the underlying cognitive basis that might mediate this genetic risk of PTSD. Here we postulate that if empathy is an index of emotional sensitivity, then individual differences in empathy may predispose an individual to differential risk of PTSD.

Empathy is the ability to identify other peoples’ mental states (their thoughts, intentions, desires, and emotions), and respond to their mental states with an appropriate emotion. Higher empathy is associated with better social and communication skills (Warrier et al., 2018a) and greater prosocial behaviors (e.g., helping others, sharing, donating) (Do et al., 2017). However, greater empathy can lead to greater risk for internalizing disorders, including depression (Tone and Tully, 2014; Tully et al., 2016). Empathy is itself partly heritable (Warrier et al., 2018a, 2018b, 2019) and increased empathy has been positively associated with both internalizing (the psychological theoretical domain to which PTSD symptoms align) (Ruggero et al., 2019) and externalizing symptoms (a primary epidemiological and genetic correlate of PTSD) (Nievergelt et al., 2019; Stein et al., 2021) leading us to hypothesize a genetic overlap between empathy and PTSD. What is not yet known is whether higher empathy polygenic scores (PGS) are associated with PTSD symptoms. We tested this using the Empathy Quotient (EQ), a self-report instrument that has been widely used and validated (Lawrence et al., 2004) and shows a partly genetic component (Warrier et al., 2018a).

To understand if empathy is genetically associated with PTSD symptom severity, we first tested for pair-wise genetic correlation among the traits of interest. Next, we evaluated how PGS for empathy

correlates with PTSD symptoms, also considering several other PGS derived from traits associated with PTSD and/or empathy (i.e., specifically, autism, depression, and anxiety). Finally, we tested which potentially traumatic experiences affect the genetic overlap between empathy and PTSD. For the first time, we report a relationship between early life events and PTSD that may be affected by the genetic effects of EQ among victims of childhood abuse/neglect. An overview is provided in Fig. 1.

2. Methods

2.1. Genome-wide Association Studies (GWAS)

The EQ GWAS consisted of participants from 23andMe, Inc. A total of 46,861 participants (24,543 females and 22,318 males) completed a 60-question self-reported assessment of cognitive and affective empathy. With high test-retest reliability (Lawrence et al., 2004), 40 questions were used to derive EQ per participant. Questions were scored from 0 to 2 for a maximum EQ of 80 (Warrier et al., 2018a).

To test if the effect of EQ on PTSD symptom severity was independent of the relationship between polygenic scores (PGS) for autism, PTSD, generalized anxiety (GAD), and depression, we included their PGS in the model of the PTSD Checklist six-item questionnaire (PCL-6). Autism<sub>PGS</sub> was derived from a GWAS of autism in 46,350 individuals (Grove et al., 2019). Depression<sub>PGS</sub> was derived from the largest non-overlapping sample of depression phenotypes consisting of 185,720 participants (Wray et al. association statistics with 23andMe and UK Biobank (UKB) removed (Wray et al., 2018)). To avoid sample overlap between base and target datasets (UKB PCL-6 overlaps with a recent large consortium GWAS of PTSD (Nievergelt et al., 2019)), we derived PTSD symptom severity PGS (PCL-17<sub>PGS</sub>) from the Million Veteran Program (MVP) GWAS of the PCL 17-item questionnaire. Respondents (N = 186,689) reported the extent to which they were affected in the previous month by symptoms in response to stressful life experiences.

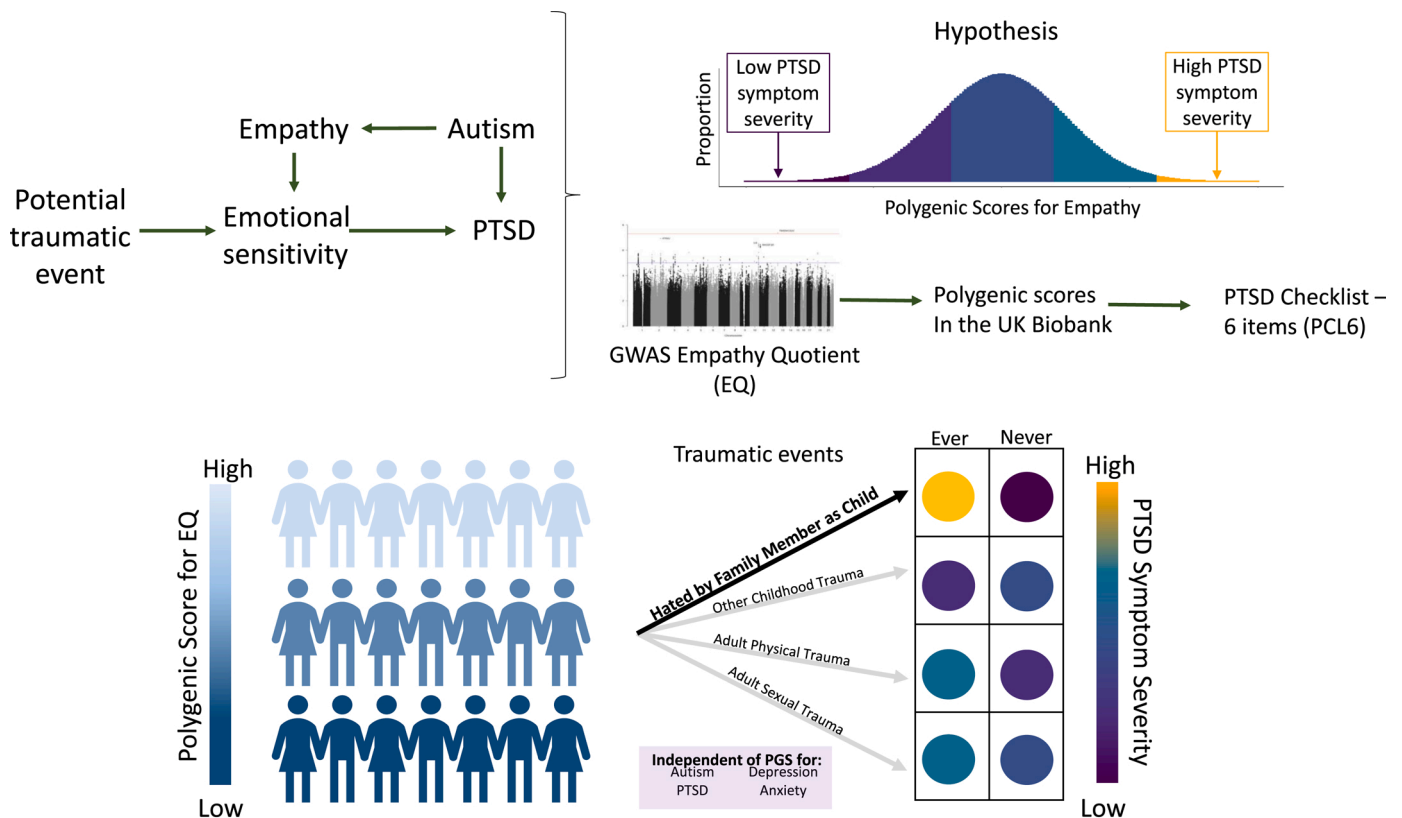


Fig. 1. Overview of study hypothesis and analytic plan.

GAD-2<sub>PGS</sub> was derived from a GWAS of GAD 2-item questionnaire in the MVP (N = 175,163). There was strong overlap between the GWAS of PCL-17 versus PCL-6 and GAD-2 versus ANGST and iPSYCH anxiety GWAS so demographic differences between the MVP and UKB were not expected to influence the use of these cohorts for PGS (Stein et al., 2021; Levey et al., 2020). We tested SNP-based heritability and the  $r_g$  between traits using Linkage Disequilibrium Score Regression (Bulik-Sullivan et al., 2015) and the 1000 Genomes Project Phase 3 European ancestry reference panel.

Details regarding the GWAS datasets used in this study are reported in Table S1.

## 2.2. Individual level data

UKB is a cohort recruited across the UK to study human health and disease. Following their initial visit, participants could respond to an online Mental Health Questionnaire (MHQ) completed by > 157,000 participants. Among relatives, we retained individuals with the higher PCL-6 score resulting in 126,219 unrelated participants of European ancestry.

PCL-6 is a summed score of six MHQ questions (Davis et al., 2020). Participants ranked the extent to which they were affected by five symptoms in the past month (0 = “Not at all” to 4 = “Extremely”). PCL-6 items are “felt irritable or had angry outbursts in the past month,” “avoided activities or situations because of previous stressful experience in the past month,” “felt distant from other people in the past month,” “repeated dis-

$$PCL6 = EQ_{PGS} + autism_{PGS} + PCL17_{PGS} + GAD2_{PGS} + depression_{PGS} + baseline\ covariates$$

turbing thoughts of stressful experience in the past month,” and “felt very upset when reminded of stressful experience in the past month.” The sixth item, “recent trouble concentrating on things,” was answered with respect to symptoms over the last two weeks (Davis et al., 2020). The PCL-6 has high sensitivity (up to 0.99) for PTSD symptoms (Nievergelt et al., 2019; Lang and Stein, 2005; Lang et al., 2012). The mean PCL-6 score was  $6.59 \pm 3.68$  and these scores were stratified into PTSD cases and controls using PCL-6 threshold >13 (N<sub>case</sub> = 11,666; N<sub>control</sub> = 114,553). (Nievergelt et al., 2019).

## 2.3. Traumatic experiences

Participants responded to 16 questions about exposure to potential traumas across their lifetime using (i) the Childhood Trauma Screener (Bellis et al., 2014; Bernstein et al., 1994; Grabe et al., 2012), and (ii) an equivalent screener for adulthood trauma developed by UKB (Davis et al., 2020). Both screeners have good test-retest reliability (Bernstein et al., 1994). Each question was ranked from 0 = “never true” to 4 = “very often true.” To overcome the relative rarity of some experiences, we binned responses into “never” (participants who responded “never true”) and “ever” (participants with any trauma endorsed). Four items (“felt loved as a child,” “someone to take you to the doctor when needed as a child,” “been in a confiding relationship as an adult,” and “able to pay rent/mortgage as an adult”) were inversely coded such that higher scores indicate more frequent experiences of the potential trauma. We derived two additional variables: (i) “any trauma” = 0 if the participant responded “Never true” to all experiences (N = 40,761) assessed in the UKB MHQ and 1 if the participant endorsed any frequency of any experience (N = 85,458) and (ii) “total number of endorsed traumas” was the summed total of all endorsed experiences (mean =  $1.46 \pm 1.53$ ).

## 2.4. Polygenic scoring

PGS were calculated in PRSice v2 (Choi and O’Reilly, 2019) using GWAS statistics clumped as follows: clump- $r^2$  (Nievergelt et al., 2019) = 0.001 in 10,000-kb windows. We identified 3,680 independent EQ SNPs, 2,434 autism SNPs, 11,137 PCL-17 SNPs, 31,967 GAD-2 SNPs, and 33,065 depression SNPs contributing to each PGS. The difference in the number of SNPs is due to the genotyping arrays and imputation procedures used in the original studies (Stein et al., 2021; Warrier et al., 2018a; Grove et al., 2019; Wray et al., 2018; Levey et al., 2020). We tested ten  $P_T$  value thresholds ( $P_T$ ):  $5 \times 10^{-8}$ ,  $1 \times 10^{-6}$ ,  $1 \times 10^{-5}$ ,  $1 \times 10^{-4}$ , 0.001, 0.05, 0.1, 0.3, 0.5, and 1. Stringent SNP clumping was applied to permit our study of the same SNPs across analyses (see Mendelian Randomization).

PRSet enrichment analysis was implemented in PRSice v2 for 5,552 Gene Ontologies (GO) from the Molecular Signatures Database (MSigDB) (Liberzon et al., 2011). Multiple testing correction was applied using a false discovery (FDR) rate of 5% to account for the correlation among the gene set annotations. PRSet used  $P_T = 1$  because it is unclear whether a gene set is associated with the phenotype when the best  $P_T$  contains a small portion of SNPs within the gene sets.

PRSice and PRSet models were performed two ways. First, we tested EQ<sub>PGS</sub>→PCL-6 with baseline covariates including principal components (PCs) of ancestry:

$$PCL6 = EQ_{PGS} + age + sex + (age \times sex) + PC_1 \dots PC_{10}$$

Second, we tested a full model including psychopathology PGS as covariates:

To contextualize the effect of EQ<sub>PGS</sub> on PCL-6 among the traumatic experiences, the fully adjusted model was further tested among participants who did and did not endorse each event (see **Traumatic Experience Definitions**).

## 2.5. Mendelian Randomization (MR)

MR uses SNPs as non-modifiable exposures to test for causality between two traits (Ebrahim and Davey Smith, 2008). The PGS  $P_T$  producing the strongest effect between traits was used to include SNPs in the analysis (Zhao et al., 2018). Inverse variance weighted (IVW) estimates were generated with *TwoSampleMR* testing two hypotheses: (i) EQ has a causal effect on PCL-17 and (ii) PCL-17 has a causal effect on EQ. To appropriately account for possible weak instrument bias, we also report the robust adjusted profile score (MR-RAPS) effect estimate. To test for effect size outliers biasing IVW or RAPS, we evaluated Cochran’s Q which tests the hypothesis that genetic instruments show no evidence of effect size heterogeneity.

## 2.6. Detecting pleiotropy among PGS SNPs

As a second test for shared genetic load between EQ and PTSD symptoms we applied a conjunctive false discovery rate using condFDR (Andreassen et al., 2013; Smeland et al., 2020). Conjunctive analysis of a PGS SNP tests whether the strength of association with EQ is independent of the strength of association with PTSD symptoms (i.e., SNP vs. EQ|PCL-17) using conditioning. Significant conjunctive  $P$ -values indicate that a SNP influences both traits independent of the

effect on the other trait.

### 2.7. Modeling PTSD diagnosis probability

Traditional gene-by-environment studies assume that genetic information (EQ<sub>PGS</sub>) and environmental variables (“felt hated as a child”) are independent (VanderWeele et al., 2010). To circumvent the small but potentially confounding relationship between EQ<sub>PGS</sub> and traumatic experiences, we modeled PTSD case status controlling for several variables. A logistic regression model of PTSD status was created using the R package effects (Fox and Weisberg, 2018). PTSD cases were defined here, and elsewhere (Nievergelt et al., 2019; Davis et al., 2020), as any individual with a PCL-6 > 13 (N<sub>case</sub> = 11,666; N<sub>control</sub> = 114,553). We sampled EQ<sub>PGS</sub> 500 times per sex per endorsement of feeling hated as a child for 2,000 total samplings at fixed effects of age, total number of traumas endorsed, autism<sub>PGS</sub>, PCL-17<sub>PGS</sub>, depression<sub>PGS</sub>, GAD-2<sub>PGS</sub>, and PCs. In this way, the sampled EQ<sub>PGS</sub> were solely used to model the probability of PTSD status among those who endorsed “ever” and “never” experiencing feeling hated as a child.

### 2.8. Identifying traumatic event correlates

To identify correlates of feeling hated as a child, we selected traits from the UKB with a priori support for an effect on PTSD. We chose all other traumatic experiences, PTSD symptoms included in the PCL-6, neuroticism score, Townsend deprivation index, income, and educational qualifications. Neuroticism score is a summary of twelve items including mood swings, fed-up feelings, etc. (Smith et al., 2013). The Townsend deprivation index is a score of regional deprivation based on unemployment, household overcrowding, and non-car and non-home ownership (Townsend et al., 1987). Average total household income before tax was binned into five strata ranging from <£18,000 to >£100,000. Educational qualifications range from other professional qualifications through college or university degree. Generalized linear models were used to test the relationship between felt hated as a child and each of the

indicated variables.

## 3. Results

### 3.1. Genetic correlation

EQ and PCL-17, GAD-2, depression, and autism GWAS had significant non-zero SNP-heritability (Table S2). Autism and PCL-17 ( $r_g = 0.342$ , s.e. = 0.089,  $P = 1.22 \times 10^{-4}$ ) were positively genetically correlated with one another but they had opposite  $r_g$  relative to EQ (PCL-17  $r_g = 0.117$ , s.e. = 0.046,  $P = 0.011$ ; autism  $r_g = -0.273$ , s.e. = 0.073,  $P = 1.84 \times 10^{-4}$ ; Fig. 2).

### 3.2. Polygenic Association of EQ and PCL-6

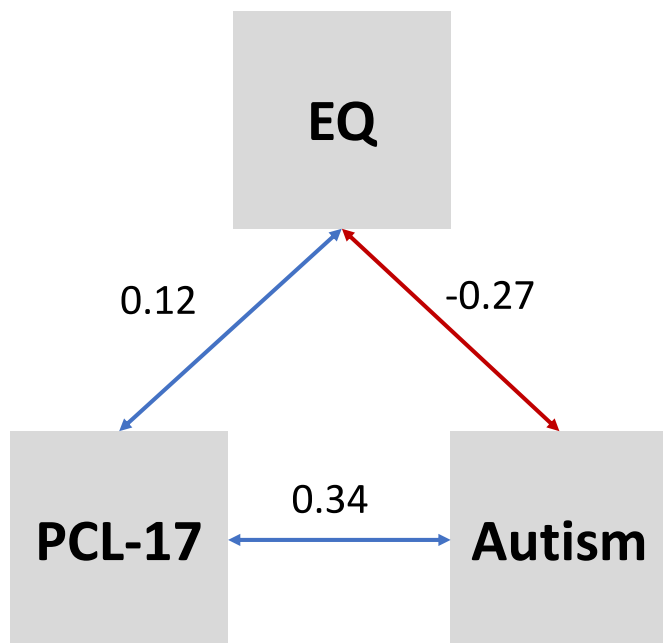
After multiple testing correction (N = 55 tests; FDR  $q < 0.05$ ; Table S3), EQ<sub>PGS</sub>, autism<sub>PGS</sub>, depression<sub>PGS</sub>, GAD-2<sub>PGS</sub>, and PCL-17<sub>PGS</sub> were associated with greater PCL-6 scores (Table 1). With respect to the EQ<sub>PGS</sub>→PCL-6, we identified suggestive evidence ( $P < 0.05$ ; Table S4) of the involvement of genes related to regulation of organelle assembly ( $R^2 = 0.009\%$ ,  $Z = 3.41$ ,  $P = 6.56 \times 10^{-4}$ ; Table S4) and signal transduction

**Table 1**

Best-fit main effects of empathizing quotient (EQ), autism, posttraumatic stress disorder 17-item questionnaire symptom count (PCL-17), depression, and generalized anxiety disorder 2-item questionnaire total score (GAD-2) polygenic scores (PGS) on PTSD Checklist 6-item summed score (PCL-6) in baseline models and models fully covaried with the inclusion of genetic load for each other psychopathology.

Base	Model	R2 (%)	P-value	P-value Threshold	P-value for effect size attenuation
EQ	Baseline*	0.012	9.35 × 10 <sup>-5</sup>	1 × 10 <sup>-5</sup>	0.992
EQ	Baseline + autism <sub>PGS</sub> + PCL-17 <sub>PGS</sub> + depression <sub>PGS</sub> + GAD-2 <sub>PGS</sub>	0.011	9.69 × 10 <sup>-5</sup>	1 × 10 <sup>-5</sup>	
Autism	Baseline*	0.012	1.10 × 10 <sup>-4</sup>	1 × 10 <sup>-6</sup>	0.880
Autism	Baseline + EQ <sub>PGS</sub> + PCL-17 <sub>PGS</sub> + GAD-2 <sub>PGS</sub> + depression <sub>PGS</sub>	0.010	2.55 × 10 <sup>-4</sup>	1 × 10 <sup>-6</sup>	
PCL-17	Baseline*	0.050	6.66 × 10 <sup>-16</sup>	0.001	0.332
PCL-17	Baseline + autism <sub>PGS</sub> + EQ <sub>PGS</sub> + GAD-2 <sub>PGS</sub> + depression <sub>PGS</sub>	0.034	2.68 × 10 <sup>-11</sup>	0.001	
Depression	Baseline*	0.102	1.62 × 10 <sup>-30</sup>	0.001	0.849
Depression	Baseline + autism <sub>PGS</sub> + EQ <sub>PGS</sub> + PCL-17 <sub>PGS</sub> + GAD-2 <sub>PGS</sub>	0.097	3.27 × 10 <sup>-29</sup>	0.001	
GAD-2	Baseline*	0.098	2.45 × 10 <sup>-29</sup>	0.3	0.511
GAD-2	Baseline + autism <sub>PGS</sub> + EQ <sub>PGS</sub> + PCL-17 <sub>PGS</sub> + depression <sub>PGS</sub>	0.081	1.12 × 10 <sup>-24</sup>	0.3	

\*Baseline model covariates were age, sex, age × sex, and the first ten within-ancestry genetic principal components



**Fig. 2.** Genetic correlation ( $r_g$ ) between the PTSD Checklist 17-item symptom count (PCL-17), Empathy Quotient (EQ), and autism. Blue and red lines indicate significant positive and negative  $r_g$ , respectively, with the magnitude of  $r_g$  labeled for each significant estimate. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

**Table 2**

Association of EQ<sub>PGS</sub> with PCL-6 in UKB participants endorsing a given traumatic experience. Covaried effects are independent of ASD<sub>PGS</sub>, depression<sub>PGS</sub>, GAD-2<sub>PGS</sub>, PCL17<sub>PGS</sub>, and number of endorsed traumas (Table S7).

Trauma ("ever" versus "never")	EQ <sub>PGS</sub> Effect			EQ <sub>PGS</sub> Covaried Effect	
	Beta (se)	P	FDR	Beta (se)	P
Felt hated by family member as a child	2.33 (0.76)	0.002	0.036	2.04 (0.073)	0.005
Physically abused by family as a child	0.89 (0.63)	0.154	0.274	–	–
Sexually molested as a child	1.27 (0.97)	0.187	0.299	–	–
Physical violence by partner or ex-partner as an adult	0.98 (0.78)	0.206	0.300	–	–
Sexual interference by partner or ex-partner without consent as an adult	2.86 (1.25)	0.022	0.116	–	–
Been in a serious accident believed to be life threatening	1.25 (0.83)	0.132	0.274	–	–
Been involved in combat or exposed to war-zone	–1.45 (1.31)	0.27	0.333	–	–
Diagnosed with life-threatening illness	0.57 (0.59)	0.331	0.353	–	–
Victim of physically violent crime	1.2 (0.58)	0.039	0.156	–	–
Witnessed sudden violent death	1.05 (0.69)	0.125	0.274	–	–
Victim of sexual assault	1.69 (0.73)	0.02	0.116	–	–
Felt loved as a child	–3.69 (3.32)	0.266	0.333	–	–
Been in a confiding relationship as an adult	1.33 (0.82)	0.107	0.274	–	–
Able to pay rent/mortgage as an adult	1.28 (1.3)	0.325	0.353	–	–
Someone to take to doctor when needed as a child*	–0.17 (1.84)	0.925	0.925	–	–
Belittlement by partner or ex-partner as an adult	0.41 (0.28)	0.139	0.274	–	–

by P53 class mediator ( $R^2 = 0.009\%$ ,  $Z = -3.44$ ,  $P = 5.93 \times 10^{-4}$ ).

We next applied two-sample MR to test for the putative causal effect between EQ and PTSD symptom severity using the largest available GWAS of PCL-17 (Stein et al., 2021). In the absence of heterogeneity and horizontal pleiotropy among 17 EQ SNPs ( $P_T < 1 \times 10^{-5}$ ), we detected no evidence of an effect linking EQ to PTSD symptom severity (Table S5). This result was not attributed to reduced power as the result persisted in MR using 2,200 LD-independent EQ SNPs in an MR-RAPS analysis (IVW  $\beta = 0.005$ , s.e. = 0.004,  $P = 0.253$  and MR-RAPS  $\beta = 0.006$ , s.e. = 0.005,  $P = 0.236$ ; Table S5). This indicates that EQ and PTSD may be linked by shared biological processes/mechanisms rather than causation.

Furthermore, although PCL-17<sub>PGS</sub> associated with EQ ( $R^2 = 0.008\%$ ,  $P = 0.016$ ,  $P_T = 1 \times 10^{-4}$ ), there was no evidence that genetically determined PCL-17 causally affects EQ ( $N = 219$  SNPs; IVW  $\beta = 0.030$ , s.e. = 0.027,  $P = 0.268$  and MR-RAPS  $\beta = 0.032$ , s.e. = 0.029,  $P = 0.269$ ; Table S5).

### 3.3. Pleiotropic Loci in EQ, PTSD symptoms, and comorbid diagnoses identified with conjunction FDR

We use conjunctive tests to identify SNPs associated with EQ and PCL-17 after conditioning each trait on the other, thereby statistically evaluating the presence of pleiotropy. One EQ-associated locus, rs11096690 (non-coding variant, conjunctive  $P = 0.007$ ) was pleiotropic with respect to EQ and PCL-17. No PCL-17 SNPs had significant conjunctive  $P$ -values. These findings support PGS results and indicate that small, yet significant, heritability is shared between EQ and PTSD symptom severity.

### 3.4. Effect of trauma type on EQ and PTSD

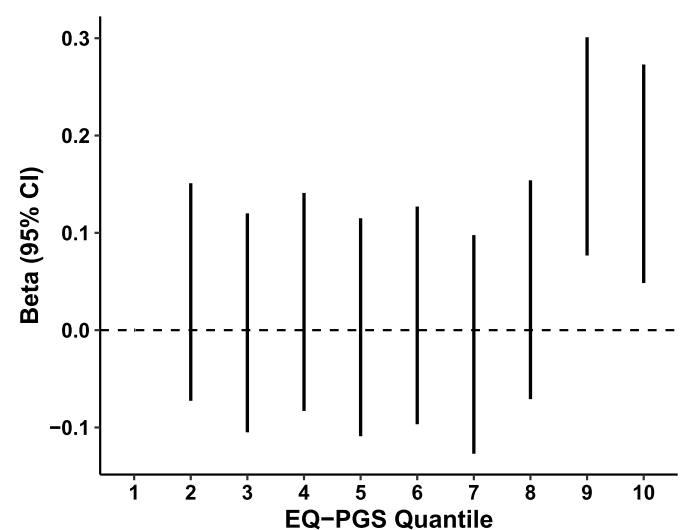
In multivariable generalized linear models among participants who experienced any trauma, the EQ<sub>PGS</sub> effected PCL-6 ( $\beta = 0.91$ , s.e. = 0.281,  $P = 0.001$ ) independently of all covariates (Table S6). There was no relationship between EQ<sub>PGS</sub> and PCL-6 in participants who report never having experienced any of the indicated potentially traumatic events, suggesting that the impact of EQ on PTSD symptoms is context specific. All subsequent analyses therefore characterize the EQ-PTSD symptom severity relationship in the context of total and specific traumatic experiences.

In multivariable models of PCL-6 that included the total number of traumas endorsed and psychopathology covariates (Table S6), EQ<sub>PGS</sub> remained associated with PCL-6 ( $\beta = 0.569$ , s.e. = 0.172,  $P = 9.34 \times 10^{-4}$ ). Participants in the highest EQ<sub>PGS</sub> decile had significantly higher PCL-6 scores ( $\beta = 0.161$ , s.e. = 0.057,  $P = 0.005$ ; Cohen's  $d = 0.037$ , 95%CI 0.013–0.062) relative to the lowest decile (Fig. 3).

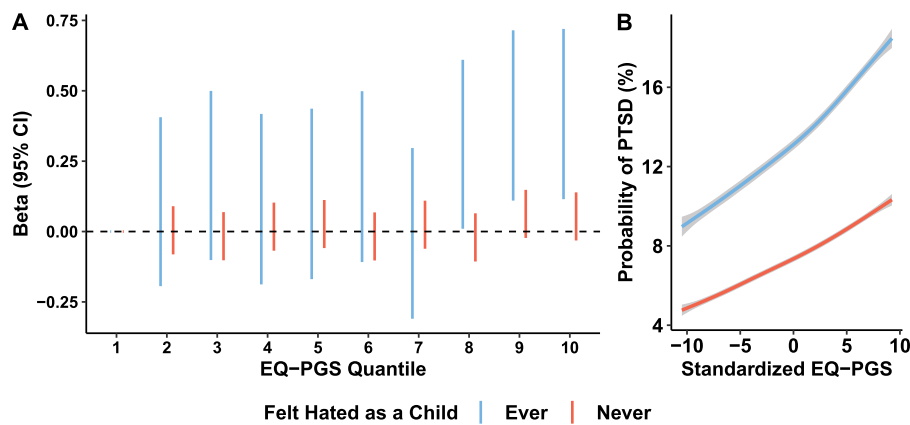
### 3.5. Contextualized effects of traumatic experiences on EQ and PTSD relationship

We next tested if the genetic effect of empathy on PTSD symptoms differs by trauma type. With univariate models of PCL-6 given EQ<sub>PGS</sub> among those who endorsed each trauma (Table S7), the experience "felt hated as a child" was the only potential trauma significant after multiple testing correction. The effect of EQ<sub>PGS</sub> on PCL-6 among those who endorsed "feeling hated as a child" was independent of all psychopathology covariates considered in this study ( $\beta = 2.04$ , s.e. = 0.727,  $P = 0.005$ ; Fig. 4 and Tables 2 and S7).

"Feeling hated as a child" was endorsed by 14.5% of participants of European descent and associated with PTSD and several quality-of-life factors (Table S8). Endorsing this experience resulted in an increased probability of PTSD case-state across the spectrum of EQ<sub>PGS</sub>. Endorsing "feeling hated as a child" interacted with EQ<sub>PGS</sub> to increase an individual's odds of PTSD diagnosis (Fig. 4). The highest probability of PTSD was 17.93% and 10.04% for those who endorsed "feeling hated as a child" and those who did not, respectively ( $P_{diff} = 0.011$ ; Cohen's  $d = 1.951$ , 95%CI 1.70–2.20; Fig. 4 and Table S9). Those in the highest decile of EQ<sub>PGS</sub> were less likely to endorse "being in a confiding adult relationship" (OR = 0.623, 95%CI 0.443–0.885,  $P = 0.007$ ) than those in the lowest decile



**Fig. 3.** Relationship between EQ<sub>PGS</sub> decile (decile 1 is the referent) and PCL-6 among UKB participants of EUR ancestry who endorsed at least one potentially traumatic experience. Effect sizes are independent of age, sex, age  $\times$  sex, total number of potentially traumatic experiences endorsed, autism<sub>PGS</sub>, PCL-17<sub>PGS</sub>, depression<sub>PGS</sub>, GAD-2<sub>PGS</sub>, and ten within-ancestry principal components. Error bars represent the 95% confidence interval around each point estimate.



**Fig. 4.** Differential effect of “feeling hated as a child” (“ever” in blue and “never” in red) on the relationship between empathizing quotient polygenic scores (EQ-PGS) and (a) PTSD symptom severity as measured by the PTSD Checklist 6-item questionnaire and (b) predicted probability of PTSD case-status and 95% confidence intervals (grey). All results are independent of age, sex, age  $\times$  sex, total number of potentially traumatic experiences endorsed, autism<sub>PGS</sub>, PCL-17<sub>PGS</sub>, depression<sub>PGS</sub>, GAD-2<sub>PGS</sub>, and ten within-ancestry principal components. Each line in (b) represents 1,000 samplings (50% female per line) of the EQ<sub>PGS</sub> at fixed covariate values. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(OR = 0.966, 95%CI 0.931–1.00,  $P = 0.071$ ;  $P_{diff} = 0.013$ ; Table S8).

#### 4. Discussion

Genetic and phenotypic overlap between psychopathology symptoms and transdiagnostic traits is common and identifying their distinct and shared liabilities is crucial to understanding co-occurring conditions and long-term prognoses. Individual differences in empathy may predispose individuals to interpret specific events as more traumatic, if higher empathy entails greater emotional sensitivity (Fernández-Abascal and Martín-Díaz, 2019). We hypothesized that common SNPs underlying empathy are a risk factor for PTSD symptom severity and that this relationship may associate with specific traumatic events. As predicted, higher EQ<sub>PGS</sub> associated with more severe PTSD symptoms, particularly in individuals who report childhood neglect/abuse.

We identified polygenic associations of EQ and PCL-6 that were independent of PGS for autism and other PTSD comorbidities; similarly, the polygenic overlap of autism and PTSD was independent of EQ<sub>PGS</sub>. The genetic overlap between autism and PTSD is in line with epidemiological data of high prevalence of PTSD among autistic individuals (Roberts et al., 2015) and recapitulates findings from genomic structural equation models. Grotzinger et al. (Grotzinger et al., 2020) reported autism loading onto a neurodevelopmental factor while PTSD loaded onto the same neurodevelopmental factor, and an internalizing factor. Although autism and PTSD are positively correlated, EQ was negatively genetically correlated with autism but positively genetically correlated with PTSD, suggesting that EQ-associated variants may have opposite effect on autism and PTSD. All three phenotypes are complex. Specifically, with PTSD, individuals must experience a potentially traumatic event and interpret it as being traumatic (suggesting emotional sensitivity). Our results suggest that the impact of empathy on PTSD is via emotional sensitivity. There is considerable evidence indicating that autistic individuals are more likely to be maltreated due to lack of understanding and safeguarding (McDonnell et al., 2019), which increases the likelihood of trauma. This complex relationship between autism, PTSD, and empathy warrants further exploration.

Genetic liability to PCL-6 exists as a continuum in the general population and by stratifying the UKB by who did or did not endorse one of the 16 traumas listed in the MHQ, we identified a unique EQ-PCL-6 relationship in the context of those who reported exposure to abuse/neglect in childhood. This was independent of psychopathology covariates and total number of traumas endorsed and was strongest in those who endorsed experiencing childhood abuse/neglect (“felt hated as a child”) (Warrier and Baron-Cohen, 2021). Endorsing this life event was associated with other child abuse/neglect and belittling behavior by an intimate partner in adulthood. There is evidence linking childhood maltreatment, adulthood interpersonal distress, and PTSD (Catani and Sossalla, 2015; Huh et al., 2014). In this study, participants in the

highest EQ<sub>PGS</sub> decile had the lowest likelihood of endorsing a secure adult relationship. These adult relationships mitigate the PGS for PTSD and fostering such relationships in adulthood may be one viable intervention among adult PTSD patients who report experiences of child abuse (Asch et al., 2021; Tamman et al., 2021).

Our study has several limitations. First, the list of traumatic experiences assessed in the UKB MHQ is not exhaustive (i.e., certain traumatic events are not included) and lacks indicators of severity, repeated instance, or which trauma was the “worst” for each participant. While we covaried for the effect of total number of events endorsed, we only marginally capture the full extent of this variable in the likely event that items occur more than once across the lifespan. One example of the complexity of this ascertainment is demonstrated by many UKB participants having PCL scores greater than zero but do not endorse any of the potentially traumatic experiences in the MHQ. This may reflect that PCL scores in trauma-unexposed individuals can also partially reflect symptoms related to depression, anxiety, and other internalizing disorders. Second, studying the relationship between early and mid-life diagnoses requires careful consideration of age of autism and PTSD diagnoses, symptom onset, and exposure to other experiences between diagnoses. While this study associates the genetic liability between two traits, the environmental conditions linking EQ to both autism and PTSD are complex. Future work in this regard requires careful identification and modeling of environmental profiles associated with these traits. Third, self-reported traumatic experiences may be incomplete, potentially limited by recall bias, and limited by temporality of memory (Yapp et al., 2021).

Despite these limitations, this study is the first, to our knowledge, to contextualize the relationship between empathy PGS and PTSD symptom severity among a set of potentially traumatic experiences. Consistent with prior reports of an autism-PTSD relationship (Levy et al., 2019), these findings provided new insight into the relationship between early life events and PTSD and the mediating/moderating effect of empathy on these relationships.

#### CRedit authorship contribution statement

**Frank R. Wendt:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **Varun Warrier:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Visualization, Funding acquisition. **Gita A. Pathak:** Writing – review & editing, Visualization. **Karestan C. Koenen:** Writing – review & editing. **Murray B. Stein:** Writing – review & editing. **John H. Krystal:** Writing – review & editing. **Robert H. Pietrzak:** Writing – review & editing. **Joel Gelernter:** Writing – review & editing. **Elizabeth V. Goldfarb:** Conceptualization, Investigation, Writing – review & editing. **Simon**

**Baron-Cohen:** Conceptualization, Methodology, Resources, Writing – review & editing, Project administration, Visualization, Funding acquisition. **Renato Polimanti:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Project administration, Visualization, Funding acquisition.

#### Declaration of competing interest

Dr. Gelernter is named as an inventor on PCT patent application #15/878,640 entitled: “Genotype-guided dosing of opioid agonists,” filed January 24, 2018. Dr. Stein is paid for his editorial work on the journals *Biological Psychiatry* and *Depression and Anxiety*, and the health professional reference *Up-To-Date*; he has also in the past 3 years received consulting income from Actelion, Acadia Pharmaceuticals, Aptinyx, Bionomics, BioXcel Therapeutics, Clexio, EmpowerPharm, GW Pharmaceuticals, Janssen, Jazz Pharmaceuticals, and Roche/Genentech, and has stock options in Oxeia Biopharmaceuticals and Epivario. Drs. Polimanti and Gelernter are paid for their editorial work on the journal *Complex Psychiatry*. Dr. Krystal reports compensation as the Editor of *Biological Psychiatry*. He also serves on the Scientific Advisory Boards for Bioasis Technologies, Inc., Biohaven Pharmaceuticals, BioXcel Therapeutics, Inc. (Clinical Advisory Board), Cadent Therapeutics (Clinical Advisory Board), PsychoGenics, Inc, Stanley Center for Psychiatric research at the Broad Institute of MIT and Harvard and the Lohocla Research Corporation. He owns stock in ArRETT Neuroscience, Inc., Biohaven Pharmaceuticals, Sage Pharmaceuticals, and Spring Care, Inc. and stock options in Biohaven Pharmaceuticals Medical Sciences, BlackThorn Therapeutics, Inc. and Storm Biosciences, Inc. He is a co-inventor on multiple patents as listed below: (1) Seibyl JP, Krystal JH, Charney DS. Dopamine and noradrenergic reuptake inhibitors in treatment of schizophrenia. US Patent #5,447,948. September 5, 1995, (2) Vladimir, Coric, Krystal, John H, Sanacora, Gerard—Glutamate Modulating Agents in the Treatment of Mental Disorders US Patent No. 8,778,979 B2 Patent Issue Date: July 15, 2014. US Patent Application No. 15/695,164: Filing Date: 09/05/2017, (3) Charney D, Krystal JH, Manji H, Matthew S, Zarate C.—Intranasal Administration of Ketamine to Treat Depression United States Application No. 14/197,767 filed on March 5, 2014; United States application or Patent Cooperation Treaty (PCT) International application No. 14/306,382 filed on June 17, 2014, (4): Zarate, C, Charney, DS, Manji, HK, Mathew, Sanjay J, Krystal, JH, Department of Veterans Affairs “Methods for Treating Suicidal Ideation”, Patent Application No. 14/197.767 filed on March 5, 2014 by Yale University Office of Cooperative Research, (5) Arias A, Petrakis I, Krystal JH.—Composition and methods to treat addiction. Provisional Use Patent Application no.61/973/961. April 2, 2014. Filed by Yale University Office of Cooperative Research, (6) Chekroud, A., Gueorguieva, R., & Krystal, JH. “Treatment Selection for Major Depressive Disorder” [filing date 3rd June 2016, USPTO docket number Y0087.70116US00]. Provisional patent submission by Yale University, (7) Gihyun, Yoon, Petrakis I, Krystal JH—Compounds, Compositions and Methods for Treating or Preventing Depression and Other Diseases. U. S. Provisional Patent Application No. 62/444,552, filed on January 10, 2017 by Yale University Office of Cooperative Research OCR 7088 US01, (8) Abdallah, C, Krystal, JH, Duman, R, Sanacora, G. Combination Therapy for Treating or Preventing Depression or Other Mood Diseases. U.S. Provisional Patent Application No. 047162–7177P1 (00754) filed on August 20, 2018 by Yale University Office of Cooperative Research OCR 7451 US01. The other authors have no competing interests to disclose.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ynstr.2022.100439>.

#### References

- Andreassen, O.A., et al., 2013. Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors. *Am J Hum Genet* 92, 197–209.
- Asch, R.H., et al., 2021. Polygenic risk for traumatic loss-related PTSD in U.S. Military Veterans: protective effect of secure attachment style. *World J. Biol. Psychiatr.* 1–24.
- Bellis, M.A., Hughes, K., Leckenby, N., Perkins, C., Lowey, H., 2014. National household survey of adverse childhood experiences and their relationship with resilience to health-harming behaviors in England. *BMC Med.* 12, 72.
- Bernstein, D.P., et al., 1994. Initial reliability and validity of a new retrospective measure of child abuse and neglect. *Am. J. Psychiatr.* 151, 1132–1136.
- Bulik-Sullivan, B.K., et al., 2015. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* 47, 291–295.
- Catani, C., Sossalla, I.M., 2015. Child abuse predicts adult PTSD symptoms among individuals diagnosed with intellectual disabilities. *Front. Psychol.* 6, 1600.
- Choi, S.W., O’Reilly, P.F., 2019. PRSice-2: polygenic Risk Score software for biobank-scale data. *GigaScience* 8.
- Davis, K.A.S., et al., 2020. Mental health in UK Biobank – development, implementation and results from an online questionnaire completed by 157 366 participants: a reanalysis. *BJPsych Open* 6, e18.
- Do, K.T., Guassi Moreira, J.F., Telzer, E.H., 2017. But is helping you worth the risk? Defining Prosocial Risk Taking in adolescence. *Developmental Cognitive Neuroscience* 25, 260–271.
- Ebrahim, S., Davey Smith, G., 2008. Mendelian randomization: can genetic epidemiology help redress the failures of observational epidemiology? *Hum. Genet.* 123, 15–33.
- Fernández-Abascal, E.G., Martín-Díaz, M.D., 2019. Relations between dimensions of emotional intelligence, specific aspects of empathy, and non-verbal sensitivity. *Front. Psychol.* 10, 1066.
- Fox, J., Weisberg, S., 2018. Visualizing fit and lack of fit in complex regression models with predictor. *Effect Plots and Partial Residuals* 87, 27.
- Goldstein, R.B., et al., 2016. The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the national epidemiologic survey on alcohol and related conditions-III. *Soc. Psychiatr. Epidemiol.* 51, 1137–1148, 2018.
- Grabe, H.J., et al., 2012. [A brief instrument for the assessment of childhood abuse and neglect: the childhood trauma screener (CTS)]. *Psychiatr. Prax.* 39, 109–115.
- Grotzinger, A.D., et al., 2020. Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic, and molecular genetic levels of analysis. *medRxiv*, 2020.09.22.20196089.
- Grove, J., et al., 2019. Identification of common genetic risk variants for autism spectrum disorder. *Nat. Genet.* 51, 431–444.
- Huh, H.J., Kim, S.Y., Yu, J.J., Chae, J.H., 2014. Childhood trauma and adult interpersonal relationship problems in patients with depression and anxiety disorders. *Ann. Gen. Psychiatr.* 13, 26.
- Lang, A.J., Stein, M.B., 2005. An abbreviated PTSD checklist for use as a screening instrument in primary care. *Behav. Res. Ther.* 43, 585–594.
- Lang, A.J., et al., 2012. Abbreviated PTSD Checklist (PCL) as a guide to clinical response. *Gen. Hosp. Psychiatr.* 34, 332–338.
- Lawrence, E.J., Shaw, P., Baker, D., Baron-Cohen, S., David, A.S., 2004. Measuring empathy: reliability and validity of the Empathy Quotient. *Psychol. Med.* 34, 911–919.
- Levey, D.F., et al., 2020. Reproducible genetic risk loci for anxiety: results from approximately 200,000 participants in the million veteran Program. *Am. J. Psychiatr.* appiajp.201919030256.
- Levy, J., Goldstein, A., Feldman, R., 2019. The neural development of empathy is sensitive to caregiving and early trauma. *Nat. Commun.* 10, 1905.
- Liberzon, A., et al., 2011. Molecular signatures database (MSigDB) 3.0. *Bioinformatics* 27, 1739–1740.
- McDonnell, C.G., et al., 2019. Child maltreatment in autism spectrum disorder and intellectual disability: results from a population-based sample. *JCPP (J. Child Psychol. Psychiatr.)* 60, 576–584.

- Nievergelt, C.M., et al., 2019. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. *Nat. Commun.* 10, 4558.
- Roberts, A.L., Koenen, K.C., Lyall, K., Robinson, E.B., Weisskopf, M.G., 2015. Association of autistic traits in adulthood with childhood abuse, interpersonal victimization, and posttraumatic stress. *Child Abuse Negl.* 45, 135–142.
- Ruggero, C.J., et al., 2019. Integrating the hierarchical taxonomy of psychopathology (HiTOP) into clinical practice. *J. Consult. Clin. Psychol.* 87, 1069–1084.
- Smeland, O.B., et al., 2020. Discovery of shared genomic loci using the conditional false discovery rate approach. *Hum. Genet.* 139, 85–94.
- Smith, D.J., et al., 2013. Prevalence and characteristics of probable major depression and bipolar disorder within UK biobank: cross-sectional study of 172,751 participants. *PLoS One* 8, e75362.
- Stein, M.B., et al., 2021. Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the Million Veteran Program. *Nat. Genet.* 53, 174–184.
- Tamman, A.J.F., et al., 2021. Attachment style moderates polygenic risk for posttraumatic stress in United States military Veterans: results from the national health and resilience in Veterans study. *Biol. Psychiatr.* 89, 878–887.
- Tone, E.B., Tully, E.C., 2014. Empathy as a "risky strength": a multilevel examination of empathy and risk for internalizing disorders. *Dev. Psychopathol.* 26, 1547–1565.
- Townsend, A., Phillimore, A., A, B., 1987. Health Deprivation: Inequality and the North. Croom Helm.
- Tully, E.C., Ames, A.M., Garcia, S.E., Donohue, M.R., 2016. Quadratic associations between empathy and depression as moderated by emotion dysregulation. *J. Psychol.* 150, 15–35.
- VanderWeele, T.J., Hernández-Díaz, S., Hernán, M.A., 2010. Case-only gene-environment interaction studies: when does association imply mechanistic interaction? *Genet. Epidemiol.* 34, 327–334.
- Warrier, V., Baron-Cohen, S., 2021. Childhood trauma, life-time self-harm, and suicidal behaviour and ideation are associated with polygenic scores for autism. *Mol. Psychiatr.* 26, 1670–1684.
- Warrier, V., et al., 2018a. Genome-wide analyses of self-reported empathy: correlations with autism, schizophrenia, and anorexia nervosa. *Transl. Psychiatry* 8, 35.
- Warrier, V., et al., 2018b. Genome-wide meta-analysis of cognitive empathy: heritability, and correlates with sex, neuropsychiatric conditions and cognition. *Mol. Psychiatr.* 23, 1402–1409.
- Warrier, V., et al., 2019. Social and non-social autism symptoms and trait domains are genetically dissociable. *Communications Biology* 2, 328.
- Wray, N.R., et al., 2018. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat. Genet.* 50, 668–681.
- Yapp, E., et al., 2021. Sex differences in experiences of multiple traumas and mental health problems in the UK Biobank cohort. *Soc. Psychiatr. Psychiatr. Epidemiol.*
- Zhao, Q., Wang, J., Hemani, G., Bowden, J., Small, D.S., 2018. Statistical Inference in Two-Sample Summary Data Mendelian Randomization Using Robust Adjusted Profile Score. *arXiv*.