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

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\textbf{ABSTRACT}

\textit{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.

\textit{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.

\textit{Results:} EQ\textsubscript{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\textsubscript{PGS} showed the strongest effect on PCL-6 (\(d = 2.32\), 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).

\textit{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.

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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 people’s 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 PGS was derived from a GWAS of autism in 46,350 individuals (Grove et al., 2019). Depression PGS 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-17PGS) 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.
GAD-2 PGS 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 > 175,000 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 disturbing 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 ± 3.68 and these scores were stratified into PTSD cases and controls using PCL-6 threshold $>13$ ($N_{\text{case}} = 11,666$; $N_{\text{control}} = 114,553$). (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 ± 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., 2015a; Grove et al., 2019; Wray et al., 2018; Levey et al., 2020). We tested ten $P$-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 PGS clumping was applied to permit our study of the same SNPs across analyses (see Mendelian Randomization).

PRSice 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 rate (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.

### 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 conjunctional false discovery rate using condFDR (Andreason et al., 2013; Smeland et al., 2020). Conjunctional 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 conjunctional $P$-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 (EQPGS) and environmental variables (“felt hated as a child”) are independent (VanderWeele et al., 2010). To circumvent the small but potentially confounding relationship between EQPGS 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 case and elsewhere (Nievergelt et al., 2019; Davis et al., 2020), as any individual with a PCL-6 case; Ncase = 11,666; Ncontrol = 114,553. We sampled EQPGS 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, autismPGS, PCL-17PGS, depressionPGS, GAD-2PGS, and PCs. In this way, the sampled EQPGS 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 (rG = 0.342, s.e. = 0.089, P = 1.22 × 10^{-5}) were positively genetically correlated with one another but they had opposite rG relative to EQ (PCL-17 rG = 0.117, s.e. = 0.046, P = 0.011; autism rG = -0.273, s.e. = 0.073, P = 1.84 × 10^{-5}; Fig. 2).

3.2. Polygenic Association of EQ and PCL-6

After multiple testing correction (N = 55 tests; FDR q < 0.05; Table S3), EQPGS, autismPGS, depressionPGS, GAD-2PGS, and PCL-17PGS were associated with greater PCL-6 scores (Table 1). With respect to the EQPGS → PCL-6, we identified suggestive evidence (P < 0.05; Table S4) of the involvement of genes related to regulation of organelle assembly (R2 = 0.009%, Z = 3.41, P = 6.56 × 10^{-4}, Table S4) and signal transduction

![Fig. 2. Genetic correlation (rG) between the PTSD Checklist 17-item symptom count (PCL-17), Empathy Quotient (EQ), and autism. Blue and red lines indicate significant positive and negative rG, respectively, with the magnitude of rG 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.)](image-url)
Table 2

Association of EQPGS with PCL-6 in UKB participants endorsing a given traumatic experience. Covaried effects are independent of ASDPGS, depressionPGS, GAD-2PGS, PCL17PGS, and number of endorsed traumas (Table S7).

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

by P53 class mediator (R^2 = 0.009%, Z = −3.44, P = 5.93 × 10^{-5}).

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_I ≤ 1 × 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 β = 0.005, s.e. = 0.004, P = 0.253 and MR-RAPS β = 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-17PGS associated with EQ (R^2 = 0.008%, P = 0.016, P_I = 1 × 10^{-5}), there was no evidence that genetically determined PCL-17 causally affects EQ (N = 219 SNPs; IVW β = 0.030, s.e. = 0.027, P = 0.268 and MR-RAPS β = 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 conjunctural 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, conjunctural P = 0.007) was pleiotropic with respect to EQ and PCL-17. No PCL-17 SNPs had significant conjunctural 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 EQPGS effected PCL-6 (β = 0.91, s.e. = 0.281, P = 0.001) independently of all covariates (Table S6). There was no relationship between EQPGS 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), EQPGS remained associated with PCL-6 (β = 0.569, s.e. = 0.172, P = 9.34 × 10^{-5}). Participants in the highest EQPGS decile had significantly higher PCL-6 scores (β = 1.61, 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 EQPGS 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 EQPGS on PCL-6 among those who endorsed “feeling hated as a child” was independent of all psychopathology covariates considered in this study (β = 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 EQPGS. Endorsing “feeling hated as a child” interacted with EQPGS 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_dif = 0.011; Cohen’s d = 1.951, 95%CI 1.70–2.20; Fig. 4 and Table S9). Those in the highest decile of EQPGS were less likely to endorse “being in a confiding adult relationship” (OR =
the polygenic overlap of autism and PTSD was independent of EQ
dependent of PGS for autism and other PTSD comorbidities; similarly,
particularly in individuals who report childhood neglect/abuse.
that this relationship may associate with specific traumatic events. As
underlying empathy are a risk factor for PTSD symptom severity and
bascal and Martín-Díaz, 2019). We hypothesized that common SNPs
dispose individuals to interpret specific events as more traumatic, if
emotional sensitivity. There is considerable evidence indicating that
activity). Our results suggest that the impact of empathy on PTSD is via
contextualize the relationship between empathy PGS and PTSD symp
ment with prior reports of an autism-PTSD relationship (Levy et al.,
maltraitment, adulthood interpersonal distress, and PTSD (Catani and
PGS) and (a) PTSD symptom severity as measured by the PTSD Checkli
t Maldonado, 2015; Warren et al., 2014). This study, participants in the
-1.00, P = 0.071; PEff = 0.013; Table S8).
0.623, 95%CI 0.443–0.885, P = 0.007) than those in the lowest decile
(OR = 0.966, 95%CI 0.931–1.00, P = 0.071; PEff = 0.013; Table S8).

4. Discussion

Genetic and phenotypic overlap between psychopathology symp
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 pre
dispose individuals to interpret specific events as more traumatic, if
higher empathy entails greater emotional sensitivity (Fernández-A
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 EQPGS 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 in
dependent of PGS for autism and other PTSD comorbidities; similarly, the polygenic overlap of autism and PTSD was independent of EQPGS. The genetic overlap between autism and PTSD is in line with epidemiological data of high prevalence of PTSD among autistic individuals (Roberts et al., 2013) 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 pop
ulation 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

![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 × sex, total number of potentially traumatic experiences endorsed, autismPGS, PCL-17PGS, depressionPGS, GAD-2PGS and ten within-ancestry principal components. Each line in (b) represents 1,000 samplings (50% female per line) of the EQPGS 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.)](image-url)
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Declaration of competing interest


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Appendix A. Supplementary data

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References


