Evidence for a shared genetic contribution to loneliness and Borderline Personality Disorder

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Abstract

Background: Loneliness, influenced by genetic and environmental factors such as childhood maltreatment, is one aspect of interpersonal dysfunction in Borderline Personality Disorder (BPD). Numerous studies link loneliness and BPD and twin studies indicate a genetic contribution to this association. The aim of our study was to investigate whether genetic predisposition for loneliness and BPD risk overlap and whether genetic risk for loneliness contributes to higher loneliness reported by BPD patients, using genome-wide genotype data.

Methods: We assessed the genetic correlation of genome-wide association studies (GWAS) of loneliness and BPD using linkage disequilibrium score regression and tested whether a polygenic score for loneliness (loneliness-PGS) was associated with case-control status in two independent genotyped samples of BPD patients and healthy controls (HC; sample 1: 998 BPD, 1545 HC; sample 2: 187 BPD, 261 HC). In sample 2, we examined associations of loneliness-PGS with reported loneliness, and whether the loneliness-PGS influenced the association between childhood maltreatment and loneliness.

Results: We found a genetic correlation between the GWAS of loneliness and BPD, a positive association of loneliness-PGS with BPD case-control status, and a positive association between loneliness-PGS and loneliness across groups. The loneliness-PGS did not moderate the association between childhood maltreatment and loneliness in BPD.

Conclusion: Our study is the first to use genome-wide genotype data to show that the genetic factors underlying variation in loneliness in the general population and the risk for BPD overlap. The loneliness-PGS was associated with reported loneliness, indicating that genetic predisposition for loneliness might contribute to BPD risk.

Keywords: Borderline Personality Disorder; Loneliness; Polygenic Score

1 Introduction

A pervasive feeling of loneliness is one aspect of interpersonal dysfunction in Borderline Personality Disorder (BPD; American Psychiatric Association, 2013). It has been discussed for a long time that loneliness is partly attributable to childhood maltreatment and to genetic factors, which is supported by the results of family and twin studies (Boomsma, Willemsen, Dolan, Hawkley, & Cacioppo, 2005; Distel et al., 2010; Matthews et al., 2016). In the recent years, genome-wide association studies (GWAS) have identified genetic variation associated with loneliness (Day, Ong, & Perry, 2018) and, to a lesser degree, with BPD (Witt et al., 2017). Despite findings from twin studies supporting a genetic correlation between BPD and loneliness, it has not yet been investigated whether the genetic variants associated with loneliness are more common in individuals with BPD. The current study uses genome-wide genetic data to assess the genetic and phenotypic overlap between loneliness and BPD and explore its association with childhood maltreatment.

Loneliness is a negative affective state resulting from the discrepancy between desired and experienced social connectedness (Peplau & Perlman, 1982). Its development is multifactorial, resulting from different environmental and biological factors (Boomsma et al., 2005). Objective social isolation may contribute to the feeling of loneliness, but is neither necessary nor sufficient to fully explain it: for example, people who are embedded in a large social network may feel lonely, while people with a small number of social contacts may not (Cacioppo et al., 2000). A short-lasting acute experience of loneliness is assumed to have a beneficial evolutionary function, promoting behaviours to reconnect to the social environment (Cacioppo, Cacioppo, & Boomsma, 2014). In contrast, long-lasting feelings of loneliness have been linked to an increased risk to health and a detrimental effect on the course of both somatic and mental disorders (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015; Mushtaq, Shoib, Shah, & Mushtaq, 2014; Pengpid & Peltzer, 2021).

While loneliness is a transdiagnostic feature of psychopathology, it plays a central role in interpersonal dysfunction in BPD: individuals with BPD often report a lack of sense of belonging and the fear of being abandoned or socially excluded (American Psychiatric Association, 2013). BPD is a personality disorder

with a lifetime prevalence of 2.7% (Trull, Jahng, Tomko, Wood, & Sher, 2010) associated with a high economic burden to the health care system and economy (e.g. Meuldijk, McCarthy, Bourke, & Grenyer, 2017). Several studies have shown increased levels of loneliness in BPD, which have been linked to smaller social networks (Liebke et al., 2017; Nenov-Matt et al., 2020). Furthermore, loneliness in BPD is linked to impairments of social-cognitive processing such as the certainty experienced during social-emotional judgments (Thome et al., 2016) and the strength of basic affiliative behaviours, such as behavioural mimicry (Hauschild et al., 2018). BPD patients describe the feeling of loneliness as a persisting state arising as early as in childhood (Sagan, 2017), suggesting that an increased propensity towards loneliness might contribute to this experience. Disorder-specific therapeutic interventions are successful in improving acute symptoms such as impulsivity or non-suicidal self-harming behaviours, but are less effective in reducing the feeling of loneliness with consequences for persistence of impairments in the patients' social functioning level (Zanarini, Frankenburg, Reich, & Fitzmaurice, 2016; Zanarini et al., 2007). Therefore, a deeper understanding of the determinants of loneliness in BPD is of particular interest to facilitate the development of therapeutic approaches that are more efficient in reducing loneliness.

In recent years, the study of genetic risk factors has received increasing attention in the study of inter-individual differences in mental health (Andreassen, Hindley, Frei, & Smeland, 2023). Twin and family studies aim to estimate the influence of genetic and environmental influences on the variation of traits or disorder risk using the information on genetic relatedness and shared family environment (Shih, Belmonte, & Zandi, 2004). In contrast, genome-wide association studies (GWAS) identify single nucleotide polymorphisms (SNPs), i.e. common changes of single base pairs in the DNA, associated with a specific phenotype. For psychiatric symptoms and disorders, the so called SNP-based heritability, i.e. the variance explained by the common variants assessed in a GWAS, usually accounts for around one third of the heritabilities estimated in twin studies (Andreassen et al., 2023). Besides insights into specific genes and pathways involved in disease etiology, GWAS also allow the estimation to what degree the association signal, and thereby the underlying genetic factors, are shared between

disorders and traits. For example, genetic correlations can be estimated using summary statistics of independent GWAS with linkage disequilibrium (LD)-score regression (Bulik-Sullivan et al., 2015). Another approach is the calculation of polygenic scores (PGS) based on the identified associations in GWAS (discovery samples) in independent target samples of healthy or affected individuals, representing the individual's propensity towards a disease or trait (Wray et al., 2014). While PGS of psychiatric phenotypes still only explain a limited amount of variance and are therefore not applicable in clinical practice, they have proven to be a useful tool in research to investigate, for example, the association of the genetic predisposition to a trait with related phenotypes.

Family and twin studies demonstrate that genetic factors contribute to BPD as well as to loneliness. The heritability of BPD is estimated to be around 46–69% (Skoglund et al., 2021; Torgersen et al., 2000), while genetic factors explain approximately 38–48% of the variance in loneliness in adults (Boomsma et al., 2005; Distel et al., 2010; Matthews et al., 2016). Analyses of shared genetic and environmental factors for borderline personality features and loneliness revealed a high genetic correlation of r = .64, but also a unique environmental correlation of r = .40 in a twin study (Schermer et al., 2020). Findings of another twin study indicated that loneliness might mainly be a consequence of the genetic determinants of BPD traits (Skaug, Czajkowski, Waaktaar, & Torgersen, 2022).

A GWAS assessing borderline personality features as a dimensional trait found a SNP-heritability of 23% (Lubke et al., 2014). Moreover, the polygenic score (PGS) for borderline personality features based on this GWAS was found to have a positive association with neuroticism (Gale et al., 2016), a personality trait associated with loneliness (Buecker, Maes, Denissen, & Luhmann, 2020). So far, one case-control GWAS, i.e. comparing BPD patients diagnosed using established diagnostic systems to controls, has been performed which did not identify associated single variants but indicated significant gene-based associations in the genes *DPYD* and *PKP4* (Witt et al., 2017). BPD was found to have positive genetic correlations with major depression, bipolar disorder, and schizophrenia (Witt et al., 2017) as well as with the personality traits neuroticism and, to a lesser degree, openness to experience (Streit et al., 2022). At the same time, a recent GWAS in the UK Biobank identified 15 genome-wide

significant loci associated with loneliness (Day et al., 2018), measured by three variables assessing the feeling of loneliness, the frequency of interacting with others and the possibility to confide in others. Associations of PGS for loneliness were found with personality traits, especially neuroticism, and a wide range of somatic but also psychiatric disorders such as mood disorders and depression in a phenome-wide association study (PheWAS; Abdellaoui, Sanchez-Roige, et al., 2019). However, this data has not been used yet to study the association of loneliness with BPD.

Childhood maltreatment has been identified a major environmental risk factor for BPD with individuals with a diagnosis of BPD being around thirteen times more likely to report childhood maltreatment than non-clinical controls (Kleindienst, Vonderlin, Bohus, & Lis, 2021; Porter et al., 2020). Some studies suggest an interaction between adverse life events and the genetic risk for mental disorders (e.g. Coleman et al., 2020; Colodro-Conde et al., 2018). Since childhood maltreatment is also related to a higher risk for perceived social isolation in adulthood (Gibson & Hartshorne, 1996; Sheikh, 2018; Shevlin, McElroy, & Murphy, 2015), childhood maltreatment might be crucial in gene-environment interactions associated with loneliness in BPD.

The aim of the present study was to investigate the genetic and phenotypic overlap between loneliness and BPD and explore its association with childhood maltreatment. For this, we analysed data from two independent genotyped BPD samples. First we used GWAS results to test the genetic correlation between a previously published GWAS sample of BPD (sample 1; Witt et al., 2017) and a GWAS of loneliness (Day et al., 2018) with LD-score regression. Furthermore, we calculated PGS for loneliness (loneliness-PGS) in sample 1 to investigate whether the loneliness-PGS is a predictor for a participant belonging to the BPD or HC group (case-control status). In sample 2, we replicated this investigation in an independent clinical sample of well-characterized patients with BPD and healthy controls (HC). In addition, we investigated associations of the loneliness-PGS with self-reported loneliness, and explored whether a genetic propensity for loneliness estimated as PGS influenced the association between the level of self-reported childhood adversity and the experience of loneliness. Furthermore, we analysed whether our findings can be explained by the genetic disposition to neuroticism, a

personality trait associated with loneliness and BPD in the past (Abdellaoui, Sanchez-Roige, et al., 2019; Buecker et al., 2020; Streit et al., 2022).

Due to the genetic correlation of loneliness with borderline personality features observed in a twin study (Schermer et al., 2020) and known association of loneliness-PGS with psychiatric disorders in a phenomewide association study (Abdellaoui, Sanchez-Roige, et al., 2019), we expected 1) a positive genetic correlation between loneliness and BPD, 2) higher loneliness-PGS in BPD cases compared to controls, and 3) a positive association of the loneliness-PGS and an individual's loneliness. Finally, we explored whether 4) the severity of childhood maltreatment predicts loneliness stronger for BPD patients with a high genetic risk for loneliness.

2 Materials and Methods

2.1 Sample 1

2.1.1 Sample Characteristics

Sample 1 consisted of a BPD GWAS sample described in detail previously in Witt et al. (2017). Briefly, controls and subjects meeting DSM-IV criteria for BPD were recruited at three academic institutions in Germany. All subjects provided written informed consent, and the study was approved by the local ethics committees. After quality control (see below), the sample consisted of 998 cases and 1545 controls.

2.1.2 Genetic correlation analysis

To obtain a point estimate of the genetic correlation of loneliness with BPD, we used LD-score regression (Bulik-Sullivan et al., 2015). LD-score regression allows the calculation of genetic correlations of GWAS that have been carried out in independent samples. Calculations were carried out with a free intercept and the European ancestry samples from the 1000 Genomes data as LD structure reference panel (The 1000 Genomes Project Consortium, 2010). Summary statistics from the GWAS of loneliness (N = 452 302; Day et al., 2018) and the GWAS of BPD (998 cases, 1545 controls; Witt et al., 2017) were used as input.

2.1.3 Polygenic Scores

For the present analyses, PGS were calculated based on an updated quality control and imputation procedure, which has been described in detail in Streit et al. (2022). Subjects were genotyped using Illumina Infinium PsychArray-24 Bead Chips (Illumina, San Diego, CA, USA). Genetic markers and subjects were filtered after the following exclusion criteria: genotypic and individual missingness (> 2%), missingness differences between cases and controls (> 2%), deviation from autosomal heterozygosity (|Fhet| > 0.2) or deviation from Hardy-Weinberg equilibrium (controls: $p < 1*10-6$, cases: $p < 1*10-10$). Additionally, subjects were excluded when they showed sex mismatches, cryptical relatedness, or were genetic outliers.

Imputation was performed with the publicly available reference panel from the Haplotype Reference Consortium (EGAD00001002729), using EAGLE/MINIMAC3 (default settings, variable chunk size of 132 genomic chunks; Das et al., 2016; Loh et al., 2016), and best-guess genotypes were used for PGS analyses.

For PGS calculation, variants in the target sample were filtered for imputation quality with an INFO score of >=0.9, and minor allele frequency of >=5%. PGS were then calculated using PRSice 2.1.6 clumping SNPs based on the p-value in the discovery samples and LD-structure in the target sample with standard settings (distance = 250kb, p = 1, $r^2 = 0.1$) (Choi & O'Reilly, 2019). PGS were calculated for loneliness (loneliness-PGS) using summary statistics from Day et al. (2018), and for neuroticism using summary statistics from Nagel et al. (2018), excluding SNPs with an INFO score <0.9 in the discovery sample. PGS were calculated for 10 p-value thresholds (PT: 5*10−8, 1*10−6, 1*10−4, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5 and 1.0; see Supplementary Table S1 for number of included SNPs). There was no sample overlap of the discovery samples with sample 1.

PRSice2 (Choi & O'Reilly, 2019) was used to calculate logistic regression models with case-control status as the dependent variable, and loneliness-PGS as a predictor of interest and the first 5 ancestry principal components (PC1–PC5) as covariates. The effect size measure, Nagelkerke's pseudo-R^2 (NkR^2), was calculated as R^2 increase when adding the PGS to a model only containing the covariates.

2.2 Sample 2

2.2.1 Sample Characteristics

A total of 448 female adult individuals who passed genetic quality control were included in the present analysis, 187 of whom met DSM-IV criteria for BPD (age *M* = 29.35, *SD* = 7.69) and 261 were healthy controls (HC, age *M* = 27.56, *SD* = 6.94). Participants of the BPD group were slightly older (t = -2.58, *p* = .010, *d* = -.25). Data on childhood traumatization was available for subsample of 409 participants (169 BPD, 240 HC), and data on loneliness for 290 individuals (155 BPD, 135 HC). For 276 subjects (144 BPD, 132 HC), both were available. Recruitment was carried out by the central project of the KFO 256, which is a clinical research unit funded by the German Research Foundation (DFG) dedicated to investigating mechanisms of disturbed emotion processing in BPD (Schmahl et al., 2014). The diagnosis of BPD according to DSM-IV was made by trained clinical psychologists using the International Personality Disorder Examination (IPDE; Loranger, 1999). All patients met at least five of the nine DSM-IV criteria for BPD.

General exclusion criteria were a lifetime history of psychotic or bipolar I disorder, current substance addiction, current pregnancy, history of organic brain disease, skull or brain damage, severe neurological illness or psychotropic medication at the time of the testing as well as a positive urine toxicology screen for illicit drugs. Additional exclusion criteria for the healthy controls were any lifetime or current psychiatric diagnoses.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Board of the University of Heidelberg. Subjects provided written informed consent prior to study participation.

2.2.2 Measures

Loneliness. Loneliness, that is the subjective experience of social isolation, was assessed using the Revised University of California Los Angeles Loneliness Scale (ULS-R; Russell, Peplau, & Cutrona, 1980; German version: Döring & Bortz, 1993). The ULS-R consists of 20 items that are rated on a 5-point Likert scale (range: 1 '*not at all*' to 5 '*totally*') combined in a sum score (range: 20–100) with higher

scores indicating higher levels of loneliness. Internal consistency for the ULS-R was α = .972 (BPD: Cronbach's α = .938; HCs: Cronbach's α = .886).

Childhood Matreatment. Severity of childhood trauma was assessed using the short form of the Childhood Trauma Questionnaire (CTQ-SF; Bernstein et al., 2003; German version: Klinitzke, Romppel, Häuser, Brähler, & Glaesmer, 2011). Subjects rated the frequency of maltreatment in childhood and adolescence in 25 items using a 5-point Likert scale (range: 1 'not at all' to 5 'very often), with sum-scores ranging from 25 to 125. Internal consistency for the CTQ-SF was α = .954 (BPD: Cronbach's α = .930; HCs: Cronbach's α = .873).

2.2.3 Genotyping, quality control and imputation

DNA was extracted from peripheral blood samples using automated DNA extraction with the chemagic Magnetic Separation Module I (Chemagen Biopolymer-Technologie, Baesweiler, Germany). All samples were genotyped using Illumina InfiniumGlobal Screening Arrays (Illumina, San Diego, CA, USA).

Genetic quality control and imputation for sample 2 was carried out in the frame of a larger ongoing BPD GWAS study (Witt et al., 2022), and was done as described for sample 1. For the present analyses, the subjects from sample 2 were extracted from the larger data set, and homogeneity of the dataset was ensured by excluding subjects >|4.5| SD on the first 20 PCs.

2.2.4 Polygenic Scores

PGS for loneliness and neuroticism were calculated and tested for association with case-control status using PRSice2 as described for sample 1. There was no sample overlap of the discovery samples with sample 2. The number of included SNPs for each p-value threshold are shown in Supplementary Table S1.

2.2.5 Statistical Analysis

The loneliness-PGS which showed the strongest association with case-control status in sample 2, PT = 0.1, was selected for further analyses in the sample. To analyse the relationship between self-reported loneliness and the loneliness-PGS, we calculated multiple linear regression analysis with the

loneliness-PGS as predictor and ULS-R score as dependent variable, controlling for the target cohort's specific principal components (PC1–PC5). To examine whether the loneliness-PGS moderates the association of the severity of childhood maltreatment and the ULS-R score in the BPD group, a moderation analysis with z-standardized predictors was performed using the PROCESS macro by Hayes (2017), which uses ordinary least squares regression, yielding unstandardized coefficients for all effects. Bootstrapping with 5000 samples together with heteroscedasticity consistent standard errors (HC3; Davidson & MacKinnon, 1993) were employed to compute the confidence intervals. In all analyses, the first five PCs were included as covariates to control for population stratification. In addition, the PGS for neuroticism (neuroticism-PGS) was included as a covariate in a second step in order to control for its often reported association to BPD and loneliness (Abdellaoui, Chen, et al., 2019).

3 Results

3.1 Genetic correlation

In the LD-score regression analysis, BPD showed a positive genetic correlation with loneliness (rg = .23 (95% CI: .046 - .42); p = .015).

3.2 PGS association with case-control status

Loneliness-PGS showed a positive association with BPD case-control status: higher loneliness-PGS were observed in the BPD cases (see Figure 1, details see Supplementary Tables S2-S7). For sample 1, the strongest association was observed for the PT = 0.5 (NkR^2 = 2.3%, $p = 2.7*10^{-12}$), and the association was replicated in sample 2 (PT = 0.1, NkR^2 = 6.6%, $p = 4.4*10^{-6}$). When adding the best fit neuroticism-PGS (both studies PT = 0.1) as a covariate, a reduced NkR^2 was observed, but the association remained significant (sample 1: PT = 0.5, NkR^2 = 0.6%, p = 0.00019; sample 2: PT = 0.1, NkR^2 = 2.7%, p = 0.0021).

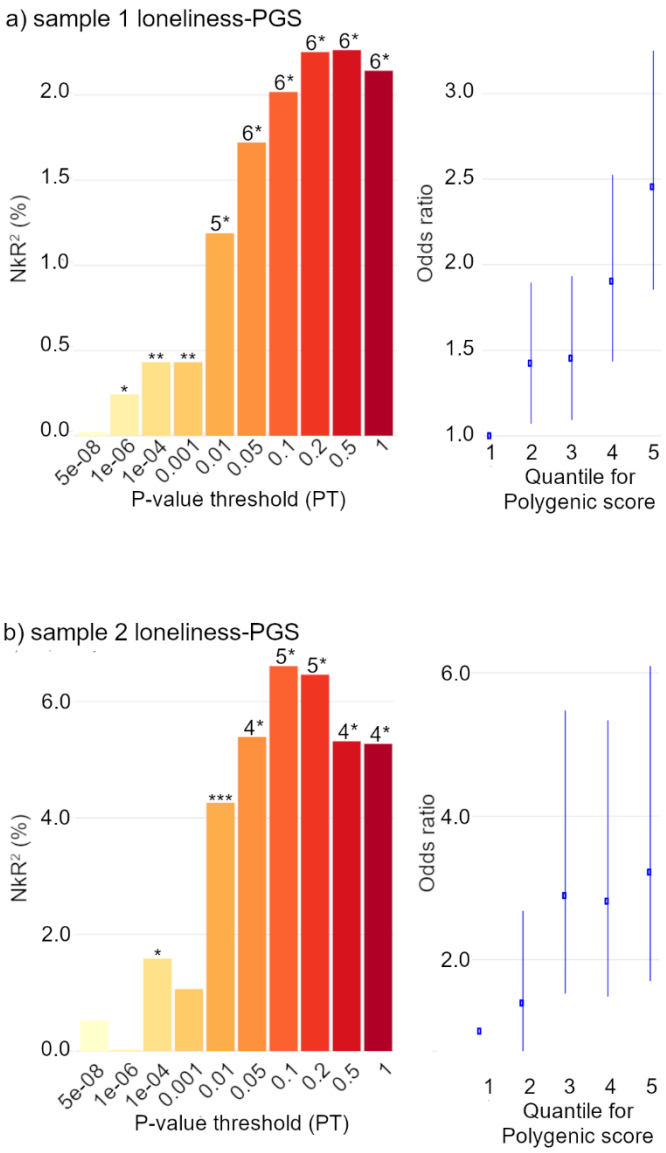

Fig. 1: Association of Loneliness Polygenic Scores (loneliness-PGS) with Borderline Personality Disorder case-control status. Left panel: Nagelkerke's R^2 describing explained variance in case-control status by PGS at ten P-value thresholds. Right panel: Odds ratio for case-control status depicted by loneliness-PGS quintile, with the first quintile as reference, depicted for the most strongly associated PT. Loneliness-PGS was based on Day et a. (2017). The number of SNPs included in the PGS are shown in Table 1. * $p < 0.05$; ** $p < 0.005$; *** $p < 0.001$; 4* $p <$ 1x10−4; 5* $p <$ 1x10−5; 6* $p <$ 1x10−8

3.3 Prediction of loneliness by loneliness-PGS

BPD patients reported a higher level of loneliness than HC (t = -4.85, $p < .001$, d = -0.465). Multiple linear regression analyses revealed that the loneliness-PGS and PCs predicted 5.8% of the variance of

the ULS-R score across groups ($F(6, 283) = 2.92$, $p = .009$, adjusted $R^2 = .038$), with the loneliness-PGS as the only significant predictor ($\beta = .185$, $p = .002$, Figure 2). This finding remained significant when we additionally controlled for the neuroticism-PGS ($F(7, 282) = 3.46$, $p = .001$, adjusted $R^2 = .056$, $\beta = .126$, $p = .046$). Separate analyses for the BPD and HC group revealed no significant relationship within the subgroups (BPD: $F(6, 148) = 1.24$, $p = .287$; HC: $F(6, 128) = 1.05$, $p = .396$, additionally controlled for neuroticism-PGS BPD: $F(7, 147) = 1.06$, $p = .390$; HC: $F(7, 127) = 0.89$, $p = .513$).

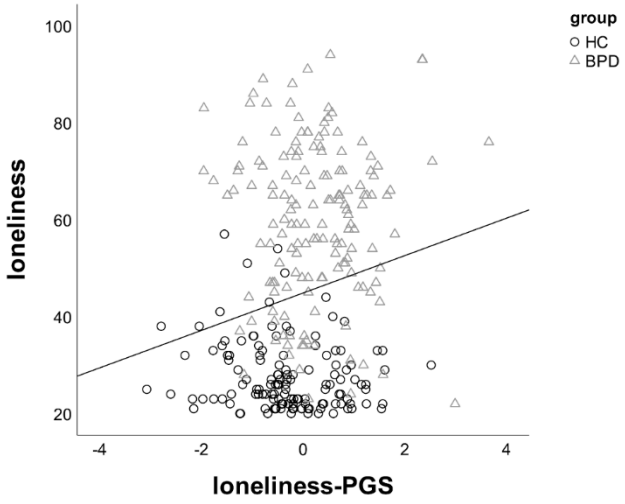

Fig. 2. Association between the standardized loneliness-PGS and loneliness assessed with the ULS-R in HC and BPD.

3.4 Exploring loneliness-PGS as a potential modulating factor of the association between childhood traumatization and loneliness in BPD

To analyse the role of the genetic risk for loneliness as a vulnerability factor that might affect, whether a higher childhood traumatization associates with a higher level of loneliness, moderation analysis was applied for the BPD group. The overall model was not significant, $F(8, 135) = 1.712$, $p = .101$, $R^2 = .103$. Results show that the loneliness-PGS did not moderate the effect between CTQ and loneliness, $\Delta R^2 = .004$, $F(1, 135) = 0.458$, $p = .500$, 95% CI[-2.484; 5.067]. This did not change with the addition of

the Neuroticism-PGS (overall $F(9,134) = 1.506$, $p = .152$, $R^2 = .104$; no interaction effect: $F(1, 134) = 0.452$, $p = .503$, $\Delta R^2 = .004$, 95% CI[-2.483; 5.038]; Table 1).

Table 1

Prediction of loneliness by childhood maltreatment and Loneliness-PGS

	B	*SE*	*t*	*p*
intercept	59.071	1.386	42.620	< .001
CTQ	3.581	1.523	2.351	.020
loneliness-PGS	-0.685	1.453	-0.471	.638
CTQ*loneliness-PGS	1.278	1.901	0.672	.503
PC1	-2.397	1.342	-1.786	.076
PC2	-0.979	1.520	-0.644	.520
PC3	-0.559	1.517	-0.369	.713
PC4	-0.855	1.378	-0.621	.536
PC5	-2.302	1.467	-1.570	.119
neuroticism-PGS	0.319	1.288	0.248	.605

Note. Predictors were z-standardized, PGS = polygenic score, CTQ = childhood trauma questionnaire

4 Discussion

The aims of the present study were to test a possible genetic overlap between loneliness and BPD, to test whether a higher genetic risk for loneliness is associated with higher loneliness experienced by BPD patients, and to test whether the genetic risk for loneliness modulates the relationship of the severity of childhood maltreatment and experienced loneliness in BPD. Therefore, we examined genetic and self-report questionnaire data of patients with a clinical confirmed diagnosis of BPD and HC. We found evidence for a genetic overlap of BPD and loneliness, indicated by the genetic correlation of the two GWAS, and the higher loneliness-PGS in the BPD groups in both samples. In addition, a higher loneliness-PGS was associated with higher loneliness in the sample 2, but did not moderate the relationship between childhood maltreatment and loneliness. The associations remained even when controlling for the neuroticism-PGS, indicating that the genetic bridge between BPD and loneliness is partly but not only explained by a genetic propensity towards neuroticism as an anxious personality trait.

The observed genetic correlation of loneliness and BPD and the positive association of the loneliness-PGS with BPD case-control status in the GWAS sample and in an independent sample indicate that the

genetic factors contributing to BPD risk and to variation in loneliness in the general population are partially shared. This is in line with former findings of a genetic association of borderline personality features and loneliness in a twin study (Schermer et al., 2020). Together with repeated findings on increased levels of loneliness and smaller social networks in BPD (Liebke et al., 2017; Nenov-Matt et al., 2020), this finding underlines the relevance of loneliness in the context of BPD. The fact that a genetic correlation has already been shown for several other somatic and psychiatric diseases (Abdellaoui, Sanchez-Roige, et al., 2019), supports prior research assuming loneliness as a transdiagnostically relevant risk factor (Holt-Lunstad et al., 2015; Mushtaq et al., 2014; Pengpid & Peltzer, 2021).

Across both groups, we found loneliness-PGS as a positive predictor of self-reported loneliness, pointing towards the relevance of a genetic vulnerability for loneliness. The small effect size suggests that other components such as actual social isolation are important factors. That this association was not significant in the subgroups could be due to the fact that HCs and BPD represent extreme groups regarding experienced loneliness, showing reduced within-group but strong between-group variance. This suggests the need for further studies that enroll participants in both groups varying more broadly in the level of loneliness. Additionally, the measures to assess loneliness differed between the GWAS study by Day et al. (2018), applying a 3 variable measure more strongly reflecting the frequency of actual social interaction, and sample 2, where subjective feelings of loneliness were assessed with the 20 item UCLA-R scale. This difference in operationalization could also partially explain the lack of association in the subgroups. Future studies on the loneliness-PGS should therefore take a more differentiated look at quantity and quality of social relationships.

In contrast to our hypothesis, the association of the severity of childhood maltreatment and reported loneliness was not moderated by the loneliness-PGS in the BPD group. While this suggests that that there are no interacting contributions of genetics and childhood maltreatment to subjective experienced loneliness, the lack of evidence may also have been caused by a lack of power due to the rather small sample.

4.1 Limitations

The present study has some limitations. First, due to the overrepresentation of women with BPD in the health care system, our results are largely based on female subjects. In sample 1, 92% of the BPD cases were female, and sample 2 consists of female participants only. Additionally, both samples were of central European ancestry. Therefore the generalisability is limited and replication in male or more balanced samples, and samples of other ancestries are needed.

Second, as already mentioned, our sample size was rather small for the investigation of the often small genetic effects. In this regard, we consider it a strength of the study, that the evidence for a shared genetic contribution to BPD and loneliness was replicated over different methods (LD-score regression and PGS analyses) and two independent samples. However, especially for the more detailed analyses in sample 2, there is need for studies replicating or extending those findings in larger samples. Larger samples would possibly allow to find effects that we could not confirm with our sample. Concurrently, larger GWAS samples, particularly for BPD, are warranted and would allow for more accurate estimations of genetic correlations, and more detailed biostatistical analyses of the shared genetics of loneliness and BPD, e.g. using methods taking both variants with equidirectional and opposing effects effect into account (Smeland et al., 2020), or applying methods such as Mendelian randomisation to allow for inference of causality (Burgess, Butterworth, & Thompson, 2013).

Third, as a self-report questionnaire, the CTQ represents a retrospective assessment of childhood experiences rather than an objective description of the exposure and experiences of adverse childhood experiences (Baldwin, Reuben, Newbury, & Danese, 2019). That should be considered in the interpretation of effects of childhood maltreatment and emphasizes the need for studies with prospective designs. Moreover, the measurement of the chronicity of loneliness might be the more appropriate tool to capture an association with genetic predispositions. Although the ULS-R is the most established instrument for measuring loneliness, originally conceptualized as a trait measure, it has been shown that most often it varies across time influenced by an individual's current state instead of being exclusively a trait (Martín-María et al., 2021).

4.2 Conclusion

Despite the limitations mentioned above, our study is, as far as we know, the first study using genome-wide genetic data to link the polygenic propensity for loneliness to BPD, finding evidence for an association in two independent samples. Further studies and larger samples are needed to further dissect the genetic overlap, investigate possible effects of different types of childhood maltreatment interacting with the loneliness-PGS and address whether the association is specific for BPD or reflects a transdiagnostically relevant association.

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7 Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The work was approved by the ethics committees of all participating institutions.

8 Competing interests

The authors declare none.

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Supplementary Material

Table S1

Number of SNPs included in PGS

	loneliness		*neuroticism*	
PT	**sample 1**	**sample 2**	**sample 1**	**sample 2**
$5x10^{-8}$	11	12	128	118
$1x10^{-6}$	36	37	275	248
0.0001	366	343	1183	1167
0.001	1363	1405	3056	3022
0.01	5730	6063	8696	8918
0.05	15,398	16,795	19,658	20,775
0.1	24,527	26,996	28,347	30,379
0.2	36,951	41,098	40,422	44,142
0.5	61,616	68,989	62,962	69,857
1	79,697	90,449	78,434	88,317

Note. Number of SNPs included for the calculation of polygenic scores (PGS) for loneliness and neuroticism at the different p-value thresholds, shown for both samples. SNP = single nucleotide polymorphism; PT = p-value threshold, PGS = polygenic score

Table S2

Prediction of BPD case-control status by Loneliness-PGS in sample 1

Threshold	***R^2***	***P***	***Coefficient***	***Standard.Error***	***Num_SNP***
5,00E-08	0,02%	0,485134	53,9157	77,2355	11
1,00E-06	0,24%	0,020836	325,338	140,782	36
0,0001	0,43%	0,002084	1892,59	614,891	366
0,001	0,43%	0,0021	4194,05	1363,58	1363
0,01	1,19%	3,83E-07	16524,5	3254,53	5730
0,05	1,72%	1,13E-09	37523,7	6161,93	15398
0,1	2,02%	4,43E-11	56111	8515,97	24527
0,2	2,26%	3,21E-12	80217,4	11512,3	36951
0,5	2,27%	2,73E-12	121418	17368,2	61616
1	2,14%	1,11E-11	150398	22143,8	79697

Note. Threshold = P value threshold, for inclusion of SNPs, R2 = Variance explained by PGS, P = P value of association, Coefficient = Coefficient of PGS association, Standard.Error = Standard error of coefficient, Num_SNP = Number of included SNPs

572 **Table S3**

573 *Prediction of BPD case-control status by Loneliness-PGS in sample 2*

Threshold	*R^2*	*P*	*Coefficient*	*Standard.Error*	*Num_SNP*
5,00E-08	0,52%	0,184573	238,21	179,536	12
1,00E-06	0,02%	0,780057	88,6995	317,641	37
0,0001	1,59%	0,020926	3028,34	1311,36	343
0,001	1,06%	0,058203	5771,3	3046,89	1405
0,01	4,26%	0,000195	27890,4	7486,94	6063
0,05	5,39%	2,99E-05	60046,1	14384,1	16795
0,1	6,60%	4,41E-06	94635,6	20613,8	26996
0,2	6,46%	5,26E-06	123476	27113,7	41098
0,5	5,32%	3,34E-05	170799	41169,9	68989
1	5,27%	3,57E-05	219538	53109	90449

574 *Note*. Threshold = P value threshold, for inclusion of SNPs, R2 = Variance explained by PGS, P = P value of
575 association, Coefficient = Coefficient of PGS association, Standard.Error = Standard error of coefficient,
576 Num_SNP = Number of included SNPs

577

578

579 **Table S4**

580 *Prediction of BPD case-control status by Neuroticism-PGS in sample 1*

Threshold	*R^2*	*P*	*Coefficient*	*Standard.Error*	*Num_SNP*
5,00E-08	1,20%	3,12E-07	0,976372	0,190851	128
1,00E-06	1,26%	1,67E-07	1,70203	0,325235	275
0,0001	1,52%	1,00E-08	5,06256	0,883501	1183
0,001	1,83%	3,20E-10	10,8374	1,72329	3056
0,01	2,93%	2,42E-15	28,3215	3,57706	8696
0,05	3,22%	1,16E-16	52,9985	6,39506	19658
0,1	3,26%	7,49E-17	69,6909	8,35724	28347
0,2	2,82%	7,29E-15	85,4205	10,9805	40422
0,5	2,80%	9,39E-15	125,074	16,1443	62962
1	2,68%	3,32E-14	151,182	19,9308	78434

581 *Note*. Threshold = P value threshold, for inclusion of SNPs, R2 = Variance explained by PGS, P = P value of
582 association, Coefficient = Coefficient of PGS association, Standard.Error = Standard error of coefficient,
583 Num_SNP = Number of included SNPs

Table S5

Prediction of BPD case-control status by Neuroticism-PGS in sample 2

Threshold	*R^2*	*P*	*Coefficient*	*Standard.Error*	*Num_SNP*
5,00E-08	1,05%	0,086132	0,858867	0,500458	118
1,00E-06	1,14%	0,062194	1,42983	0,7667	248
0,0001	2,95%	0,001887	6,24455	2,00948	1167
0,001	2,87%	0,002042	11,6664	3,78271	3022
0,01	5,11%	4,52E-05	31,9979	7,84412	8918
0,05	4,94%	6,07E-05	59,0445	14,7243	20775
0,1	7,20%	1,62E-06	97,3458	20,3	30379
0,2	5,93%	1,21E-05	116,457	26,6188	44142
0,5	6,64%	3,82E-06	185,185	40,0769	69857
1	6,68%	3,58E-06	233,764	50,4433	88317

Note. Threshold = P value threshold, for inclusion of SNPs, R2 = Variance explained by PGS, P = P value of association, Coefficient = Coefficient of PGS association, Standard.Error = Standard error of coefficient, Num_SNP = Number of included SNPs

Table S6

Prediction of BPD case-control status by Loneliness-PGS in sample 1, adjusted for Neuroticism-PGS

Threshold	*R^2*	*P*	*Coefficient*	*Standard.Error*	*Num_SNP*
5,00E-08	0,00%	0,928028	7,09112	78,5055	11
1,00E-06	0,05%	0,285938	153,727	144,064	36
0,0001	0,07%	0,214689	788,579	635,554	366
0,001	0,01%	0,661796	633,814	1448,93	1363
0,01	0,19%	0,036556	7364,58	3522,57	5730
0,05	0,34%	0,005847	18823,3	6829,29	15398
0,1	0,47%	0,001084	30925,7	9464,2	24527
0,2	0,62%	0,000199	47475,4	12762,2	36951
0,5	0,62%	0,000193	71895,5	19283,9	61616
1	0,55%	0,000458	86204,7	24600,3	79697

Note. Threshold = P value threshold, for inclusion of SNPs, R2 = Variance explained by PGS, P = P value of association, Coefficient = Coefficient of PGS association, Standard.Error = Standard error of coefficient, Num_SNP = Number of included SNPs

596 **Table S7**

597 *Prediction of BPD case-control status by Loneliness-PGS in sample 2, adjusted for Neuroticism-PGS*

Threshold	*R^2*	*P*	*Coefficient*	*Standard.Error*	*Num_SNP*
5,00E-08	0,22%	0,62118	160,864	325,517	12
1,00E-06	0,00%	0,925435	-42,5059	454,172	37
0,0001	0,67%	0,157369	2102,7	1487,08	343
0,001	0,15%	0,493603	2327,8	3400,28	1405
0,01	1,58%	0,020136	18676,5	8037,06	6063
0,05	1,97%	0,00903	40811,2	15631,1	16795
0,1	2,73%	0,002126	68385,9	22260,9	26996
0,2	2,60%	0,00264	88055,8	29285,1	41098
0,5	1,78%	0,012332	111941	44731,7	68989
1	1,73%	0,013757	142390	57799,1	90449

598 *Note*. Threshold = P value threshold, for inclusion of SNPs, R2 = Variance explained by PGS, P = P value of
599 association, Coefficient = Coefficient of PGS association, Standard.Error = Standard error of coefficient,
600 Num_SNP = Number of included SNPs