Borderline Personality Disorder and the Big Five: Molecular Genetic Analyses Indicate Shared Genetic Architecture with Neuroticism and Openness

Fabian Streit (fabian.streit@zi-mannheim.de)
University of Heidelberg https://orcid.org/0000-0003-1080-4339
Stephanie Witt
University Medical Centre Mannheim https://orcid.org/0000-0002-1571-1468
Swapnil Awasthi
Jerome Foo
Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg
Martin Jungkunz
Josef Frank
Central Institute for Mental Health https://orcid.org/0000-0003-4867-9465
Lucia Colodro-Conde
Guy Hindley
University of Oslo https://orcid.org/0000-0003-1666-4701
Olav Smeland
Tolou Maslahati
Cornelia Schwarze
Björn Schott
Annette Hartmann
Ina Giegling
Lea Zillich
Lea Sirignano
Central Institute of Mental Health https://orcid.org/0000-0002-7989-5833
Eric Poisel
Chi-Hua Chen
Markus Nöthen
School of Medicine & University Hospital Bonn https://orcid.org/0000-0002-8770-2464
Arian Mobascher
Dan Rujescu
Klaus Lieb
University Medical Center Mainz
Norbert Dahmen

Stefan Roepke
Christian Schmahl
Central Institute of Mental Health
Martin Bohus
Stephan Ripke
Charite Universitaetsmedizin Berlin, Dept. of Psychiatry and Psychotherapy
Marcella Rietschel
University of Mannheim https://orcid.org/0000-0002-5236-6149
Ole Andreassen
University of Oslo https://orcid.org/0000-0002-4461-3568

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Abstract

Both environmental (e.g. interpersonal traumatization during childhood and adolescence) and genetic factors may contribute to the development of Borderline Personality Disorder (BPD). Twin studies assessing borderline personality symptoms/features in the general population indicate that genetic factors underlying these symptoms/features are shared in part with the personality traits of the Five Factor Model (FFM) of personality – the “Big Five".

In the present study, the genetic overlap of BPD with the Big Five -Openness to Experience, Conscientiousness, Extraversion, Agreeableness and Neuroticism- was assessed. Linkage disequilibrium score regression was used to calculate genetic correlations between a genome-wide association study (GWAS) in central European populations on BPD (N = 2,543) and GWAS on the “Big Five” (N = 76,551–122,886, Neuroticism N = 390,278). Significant positive genetic correlations were found between BPD and the traits Neuroticism (rg=.34, p=6.3*10^{-5}) and Openness (rg=.24, p=.036), but not between BPD and the other personality traits (all |rg|<.14, all p>.30). A cluster and item-level analysis showed positive correlations with the Neuroticism clusters “Depressed Affect” and “Worry”, and with a broad range of Neuroticism items (N = 348,219 – 376,352).

The observed associations indicate a partially shared genetic background of BPD and the personality traits Neuroticism and Openness. Larger GWAS of BPD and the “Big Five” are needed to further explore the role of personality traits in the etiology of this disorder.

Introduction

Borderline Personality Disorder (BPD) is a complex psychiatric disorder characterized by affective instability, identity disturbance and interpersonal difficulties, and it is associated with high rates of self-injury and suicidal behaviors (Association 2013; Soloff and Chiappetta 2019). It has been proposed that variants of normal personality traits contribute to the presentation of personality disorders (Costa Jr and McCrae 1990; Trull and Widiger 2013; Widiger and Costa Jr 2013). This is also reflected in the introduction of the alternative DSM-5 model for personality disorders, i.e. that personality disorders are characterized by impairments in personality functioning and pathological personality traits and is also represented in the current concept of the ICD-11. The alternative DSM-5 model includes the domains of negative affectivity, detachment, psychoticism, antagonism, and disinhibition, which are variants of the five domains of the Big Five or the Five Factor Model (FFM) of personality (APA, 2013). The specific personality disorder diagnoses that can be derived from this model include antisocial, avoidant, borderline, narcissistic, obsessive-compulsive, and schizotypal personality disorders (Association 2013). The Big Five -Openness to Experience (hereafter Openness), Conscientiousness, Extraversion, Agreeableness and Neuroticism- each with six subdimensions or facets (McCrae et al. 1998) can be measured with instruments like the Revised NEO Personality Inventory (NEO-PI-R, Costa Jr and McCrae 1992). In the case of BPD, Lynam & Widiger (2001) proposed a combination of high scores in specific Neuroticism and Openness facets and low scores in Agreeableness and Consciousness facets to

distinguish those with BPD from others. This proposal has been confirmed in further studies (Samuel and Widiger 2008).

Twin studies show that the expression of the “Big Five” personality traits is substantially influenced by genetic factors, with heritability estimates of 40-60% for different traits (Bouchard Jr and McGue 2003; Vukasović and Bratko 2015). Genetic factors also influence the risk for BPD: twin and family studies estimate the heritability to be around 46% (Skoglund et al. 2021) or 69% (Torgersen et al. 2000), indicating that besides well-established environmental risk factors such as early trauma or abuse (Bohus et al. in press; Lieb et al. 2004), the genetic background of an individual modulates their risk to develop BPD (Leichsenring et al. 2011). Moreover, twin studies indicate that the genetic factors underlying personality disorders and the Big Five personality traits are substantially shared (Czajkowski et al. 2018; Kendler, Myers, and Reichborn-Kjennerud 2011; Distel et al. 2009) primarily indicating positive genetic correlations with Neuroticism, and negative genetic correlations with Agreeableness and Conscientiousness. More studies to investigate the overlap between the genetic factors influencing personality traits and those increasing the risk for personality disorders, including BPD, are needed (Nia et al. 2018; Streit et al. 2020).

To further investigate the genetic overlap between personality traits and personality disorders observed in twin studies, data from genome-wide association studies (GWAS) can be used. GWAS systematically investigate the genetic underpinnings of a disorder or trait, by investigating the association of several million single nucleotide polymorphisms (SNPs)—common variations of one single nucleotide in the genetic code—with the phenotype of interest. The largest GWAS meta-analysis to date examining all Big Five personality traits (Lo et al. 2017; N = 76,551–122,886), identified SNPs associated with Neuroticism, Consciousness, and Extraversion after rigid correction for multiple testing (= $5*10^{-8}$). More importantly, it showed a significant SNP-based heritability—the variance explained by the entirety of the investigated SNPs for all five personality traits (8.5% – 18%). A genetic principal component analysis showed the Big Five traits of Neuroticism and Openness to cluster with the genetics underlying several psychiatric disorders including affective disorders and Schizophrenia (SCZ) (Lo et al. 2017). A larger GWAS meta-analysis for Neuroticism including data from the UK Biobank (UKB) published shortly after (Nagel, Jansen, et al. 2018; N = 449,484) identified 136 independent associated genetic loci. Detailed analyses in the UK-Biobank subset (N = 348,219-376,352) where the 12-item Neuroticism scale of the EPQ-R (Eysenck, Eysenck, and Barrett 1985) was applied, found evidence for substantial genetic heterogeneity within the scale of Neuroticism (in heritability and genetic association with other phenotypes) (Nagel, Watanabe, et al. 2018). The authors identified two genetically distinguishable clusters of 4 items each, which were labeled “Depressed Affect” and “Worry”. Those clusters showed distinct genetic correlational patterns with other GWAS, notably also of mental disorders (Nagel, Jansen, et al. 2018; Nagel, Watanabe, et al. 2018), indicating that (genetic) analysis of personality traits should not be limited to the sum-score level.

Witt et al. (2017) performed the first BPD case-control GWAS, comparing 998 patients with a diagnosis of BPD to 1,545 controls. They did not observe associations on the level of single variants at the genome-wide significance level, but demonstrated that BPD has positive genetic correlations with Major

Depressive Disorder (MDD), Bipolar Disorder (BD) and SCZ using linkage disequilibrium (LD) score regression. So far, molecular genetic approaches have not been used to investigate the association of BPD with the Big Five.

Our aim was to test whether the genetic variants associated with the risk of developing BPD are partially shared with the genetic variants associated with the Big Five personality dimensions. Therefore, we tested the genetic correlation of the BPD-GWAS by Witt et al. (2017) with the Big Five GWAS by Lo et al. (2017) except for Neuroticism, where we used the larger GWAS from Nagel et al. (Nagel, Watanabe, et al. 2018). To explore the association of BPD with Neuroticism in a more detail, cluster and item-based genetic correlations were calculated for Neuroticism (Nagel, Jansen, et al. 2018; Nagel, Watanabe, et al. 2018).

Methods

We applied LD score regression (Bulik-Sullivan et al. 2015), a method that incorporates information on the LD structure to estimate SNP-heritability and genetic correlations. LD score regression was carried out using a free intercept, and the 1000 Genomes data set served as a reference panel for underlying LD structure (Genomes Project Consortium 2010). An overview of the used GWAS statistics can be found in Table 1.

In a first step, the genetic correlations from GWAS results using the BPD-GWAS (Witt et al. 2017) (N = 2,545) and the Big Five were calculated. For the Big Five the data from Lo et al. (2017; N = 76,551–122,886) was used, with the exception of Neuroticism, for which the larger meta-analysis by Nagel et al. was used (Nagel, Watanabe, et al. 2018; N = 390,278 excluding data from 23andMe Inc.).

In a second step, to assess genetic correlations of BPD with Neuroticism clusters and items, we analyzed the genetic correlation of BPD (Witt et al. 2017) with the respective GWAS summary statistics from Nagel et al. based on the UKB (Nagel, Jansen, et al. 2018; Nagel, Watanabe, et al. 2018; N = 348,219 - 376,352; UKB item codes 1920-2030).

Bonferroni corrected alpha levels were applied to the respective tests (BPD and BIG-5: $\alpha = 0.0033$ (0.05/15 tested correlations; BPD and Neuroticism clusters/items $\alpha = 0.0036$ (0.05/14 tested correlations).

Table 1
Overview of GWAS summary statistics analyzed

Phenotype	Total N	Sample	Reference	See
Borderline Personality Disorder	2545	GBGC	(Witt et al. 2017)	Figure 1, Fig. 2
Openness	76,581	23andMe and GPC	(Lo et al. 2017)	Figure 1
Conscientiousness	76,551			
Extraversion	122,886			
Agreeableness	76,551			
Neuroticism				
Sum score	390,278	UKB and GPC	(Nagel, Jansen, et al. 2018)	Figure 1
Sum score UKB	380,506	UKB	(Nagel, Watanabe, et al. 2018)	Figure 2
Clusters	348,219 - 357,957	UKB	(Nagel, Jansen, et al. 2018)	Figure 2
Single items	366,726 - 376,352	UKB	(Nagel, Watanabe, et al. 2018)	Figure 2

Note: GBGC = German Borderline Genomics Consortium, GPC = Genetics of Personality Consortium, UKB = UK Biobank

Results

As shown in Figure 1, significant positive genetic correlations were observed between Agreeableness, Conscientiousness, Extraversion and Openness, with the exception of a negative correlation of Conscientiousness with Openness. Neuroticism was negatively correlated with the other personality traits of the Big Five. The correlational patterns correspond largely to those reported in Lo et al. (2017), even when using the larger Neuroticism GWAS meta-analysis by Nagel et al. (2018).

For BPD, the LD-score regression SNP-heritability estimate was 50.3% (95% CI = 17,9%-85,3%) on the liability scale for a population prevalence of 3% (Ellison et al. 2018; Jørgensen et al. 2013). BPD showed a statistically significant positive genetic correlation with Neuroticism (rg=.34, p=6.3*10^{-5}) and nominally significant correlation with Openness (rg=.24, p=0.036) (see Figure 1 and Table 2). No significant genetic correlations were observed with the other Big Five traits.

– Figure 1 about here –

Table 2
Genetic correlations of Borderline Personality Disorder with Big Five personality traits

Big Five Trait	*rg*	*se*	*z*	*p*
Agreeableness	0.14	0.14	1.03	0.30
Conscientiousness	-0.05	0.11	-0.41	0.68
Extraversion	0.02	0.10	0.22	0.83
Neuroticism#	0.34**	0.08	4.00	$6.3*10^{-5}$
Openness	0.24*	0.11	2.09	0.04

Note: * p < 0.05, ** p < 0.0033 (0.05/15 tested correlations), #based on (Nagel, Watanabe, et al. 2018), the other BIG-5 personality traits were based on (Lo et al. 2017)

– Figure 2 about here –

Both the “Depressed Affect” cluster (rg = .35, $p = 1.5*10^{-4}$), and the “Worry” cluster (rg = .28, $p = 1.7*10^{-3}$) were significantly associated with BPD. On a single item-level, some degree of heterogeneity of the genetic correlation of BPD with Neuroticism was observed. While all observed genetic correlations were positive, the correlations ranged from 0.10 to 0.45. With items from the “Depressed Affect” cluster, BPD showed the strongest associations with the items “mood swings” and “miserableness”. From the “Worry” cluster, only the correlation with “tense / ‘highly strung’” was significant after correction for multiple testing. From the items not assigned to either of the clusters, “sensitivity / hurt feelings” showed the strongest correlation with BPD (see Figure 2).

Discussion

The present study is the first to use molecular genetic data to investigate shared genetic factors between diagnosed BPD and the Big Five personality traits, showing a genetic correlation of BPD with the trait Neuroticism and a suggestive correlation with Openness. These results provide biological evidence that partially supports the concept that associates variants of normal personality traits and the presence of BPD. Specifically, it supports the description of BPD as high levels of neuroticism and openness, although the original proposal includes also low levels of agreeableness and conscientiousness (Lynam & Widiger, 2001).

The observed genetic correlation of BPD and Neuroticism is in line with findings from twin and family studies, showing a positive genetic overlap of Neuroticism and Borderline Personality Features (Distel et al. 2009), a continuous measure of borderline personality assessed with the Personality Assessment Inventory–Borderline Features scale (PAI-BOR) which can be used in the general population (Morey 1991) or BPD DSM-IV Criterion counts (Czajkowski et al. 2018). A polygenic risk score summarizing the genetic risk burden for Borderline Personality Features (Lubke et al. 2014) was associated with Neuroticism

(smallest $p=5.43*10^{-7}$) in a target sample of >100,000 subjects from the general population (Gale et al. 2016), supporting a genetic relation between both phenotypes.

Phenotypic studies implicate that Neuroticism increases risk for most psychiatric disorders (Caspi et al. 2014; Lahey 2009; Ormel et al. 2013). It is likely that a genetic disposition to Neuroticism also contributes to genetic correlations between many psychiatric disorders (Anttila et al. 2018) and the observed comorbidities (Grant et al. 2008). With respect to depression, strong genetic correlations of Neuroticism with both depressive symptoms in the general population as well as with clinical MDD have been observed (Lo et al. 2017; Wray et al. 2018). As a broad genetic risk factor, Neuroticism might link BPD to other (comorbid) psychiatric conditions as well as other personality disorders (Krueger 2005). Supporting this, a twin study showed that the finding of a genetic association between Borderline Personality Features and substance use disorders, is attributable to variation in personality factors, especially Neuroticism (Few et al. 2014).

Neuroticism comprises facets which are characteristic clinical features of BPD personality, such as emotional lability, anxiousness, angry hostility, depressiveness, and vulnerability (e.g. Trull and Widiger 2013). In the present study, BPD showed similar correlations with both tested Neuroticism clusters, with slightly a higher correlation for “Depressed Affect”. In the item-based analysis, all 12 items showed a positive correlation with BPD, with nominal significance for 10, and significance after Bonferroni correction for four of the 12 items. The results indicate that a rather broad range of aspects of Neuroticism contributes to BPD, similar to depression and anxiety, and distinct from disorders such as schizophrenia, anorexia nervosa or attention deficit hyperactivity disorder, which show primarily association with one of the two clusters (Nagel, Watanabe, et al. 2018). Notably, the most strongly correlated item was “mood swings” which has previously been used as a measure of mood instability (Ward et al. 2020), a core symptom of BPD (Koenigsberg 2010). “Mood swings” has shown extensive genetic overlap with a range of mental disorders, with the strongest positive correlations being reported for depression, anxiety, ADHD and PTSD (Ward et al. 2020; Hindley et al. 2021). Future research should further investigate how single items, and specific clusters of these features contribute to different psychiatric disorders (Mõttus et al. 2020).

Less is known about the genetic correlation of Openness with BPD and other psychiatric disorders, although high level of Openness to feelings and to actions have been proposed to characterize BPD (Lynam and Widiger 2001). In twin studies, Openness for Experience showed a moderate genetic correlation with DSM-IV Criterion counts for BPD (r=.24) (Czajkowski et al. 2018) but no evidence for a genetic correlation with Borderline Personality Features (Distel et al. 2009). Using a molecular genetic approach, we observed a nominally significant genetic correlation (rg=.24). These disparities may be attributable to the different instruments used in the studies, or to the fact that the present results are based on a sample of patients fulfilling the diagnosis of BPD (Witt et al. 2017), and not on normal variation observed in Borderline Personality Features in unaffected subjects. It is unclear however, if this might entail differences in statistical power, or in the underlying genetic architecture.

While Openness is generally considered a beneficial personality trait, in high levels and in combination with other traits it might be disadvantageous and increase the risk for certain psychiatric disorders (Trull 2012). The present results suggest that increased Openness and BPD might be influenced by overlapping genetic factors. Openness has for example been associated with aspects of risk-taking including substance use (Booth-Kewley and Vickers Jr 1994; Nicholson et al. 2005), and increased risk-taking is a characteristic feature of BPD which contributes strongly to the impairment experienced by affected patients and their relatives. Furthermore, both Openness (Larøi et al. 2005) and BPD (Slotema et al. 2012) are associated with hallucinations; shared genetic variants associated might underlie these associations. Openness has been shown to be genetically associated to other psychiatric disorders such as BD and SCZ (Lo et al. 2017), and BPD and SCZ share a sizable fraction of genetic risk factors (Witt et al. 2017). Still, compared to Neuroticism, Openness has been less strongly linked with BPD, and while all facets of Neuroticism are related to the BPD phenotype, only Openness to feelings and actions do (Trull 2012). In regard to the association of BPD with other Big Five traits, there are inconsistencies with previous studies: the results of twin studies (Czajkowski et al. 2018; Distel et al. 2009) and clinical observations (Trull 2012) indicate a negative association of Borderline Personality with Agreeableness and Conscientiousness, whereas we observe genetic correlations close to zero.

There are some limitations to the study: First, while BPD showed genetic correlations with two of the Big Five, the effects and the statistical significance of the results are limited in the case of Openness, where the association did not survive correction for multiple testing. Larger samples are needed to confirm and expand the observed associations: despite being the largest available samples for the phenotypes, the samples for the Big Five and especially, the BPD GWAS are limited in size. Increased sample sizes will be able to provide more reliable estimates of the underlying genetic risk variants. The sample of BPD is drastically smaller compared to those of other psychiatric disorders such as MDD (Howard et al. 2019), BD (Mullins et al. 2021) and SCZ (Ripke et al. 2020). Clinicians and researchers in the field of BPD should work together to facilitate the generation of larger BPD case-control samples for genetic studies. Second, we assessed genetic correlations to assess shared genetic overlap. However, more complex genetic overlap, with a mix of agonistic and antagonistic shared effects can remain undetected by this approach, as it has been shown e.g. for bipolar disorder and cognition (Smeland et al. 2020). Third, different personality inventories were used in the different studies to assess the personality traits. However, high genetic correlations were reported for the personality traits between the samples (Lo et al. 2017; Nagel, Jansen, et al. 2018; all rg > .83). Fourth, the available samples were all from European ancestry, which limits the transferability of the results to other populations. Fourth, the GWAS by Lo et al. (Lo et al. 2017) investigated sum scores of personality domains, but did not investigate the respective facets. While our cluster and item-based analyses for Neuroticism indicate specific contributions of personality clusters/facets, no item-based data was available to us for the other Big Five traits. Future genetic studies of BPD and the Big Five and should assess the Big Five and their facets in more detail.

The present study shows the applicability of molecular genetic approaches to investigating the extent to which common genetic factors underlie personality traits and BPD. Future research should extend the present analysis, by leveraging data from large and well characterized samples. Besides detailed

analyses of the underlying personality facets, future research should investigate functional domains involved in BPD and the Big Five, as formulated in the Research Domain Criteria (RDoC) approach (Insel 2014). The present study investigated genetic associations of BPD with the Big Five. It should be noted that environmental factors such as early or recent trauma and chronic stress, which are highly important contributors to BPD (Bohus et al. in press; Lieb et al. 2004; Zimmerman and Choi-Kain 2009), influence the development of personality not only in early age, but also throughout the entire lifetime (Briley and Tucker-Drob 2017). Identifying and assessing the relevant aspects of environmental exposure suspected to modify biological pathways is a major challenge, especially when the pathways are thought to link normal variation in personality traits to personality disorders. Future studies integrating environmental aspects in as much detail and as reliably as possible will be able to further address the interplay of environmental and genetic factors in the analyses (e.g. Colodro-Conde et al. 2018; Coleman et al. 2020).

In summary, the present study gives the first molecular genetic insight into the shared genetic factors underlying BPD and normal variation in the Big Five personality traits and supports the relationship of BPD and Neuroticism. Future studies may extend this approach to the specific underlying genetic variants and other psychiatric conditions, thereby helping to further elucidate the relationship between psychopathology and normal variability of human personality.

Declarations

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The authors have nothing to disclose.

Author Contributions

Planned the investigation: FS, SHW, MR, OAA, MB, CS

Acquired data: TM, CS, ND, BS, AH, IG, AM, DR, KL, SR, CS, MB, FS, SHW, JF, MR

Developed the analysis plan: FS, SHW, MR, GH, OAA, SA, SR

Performed statistical analyses: FS, SA, EP, MJ, JF, OS, SR,

Reviewed the literature for the paper. FS, SHW, MR, OAA, LCC, GH, LS, LZ, LCC

Drafted the manuscript. FS, SHW, MR, JCF, LCC

All authors contributed, revised, and edited the final manuscript critically. All authors agreed to the publication of the final version of the manuscript.

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Figures

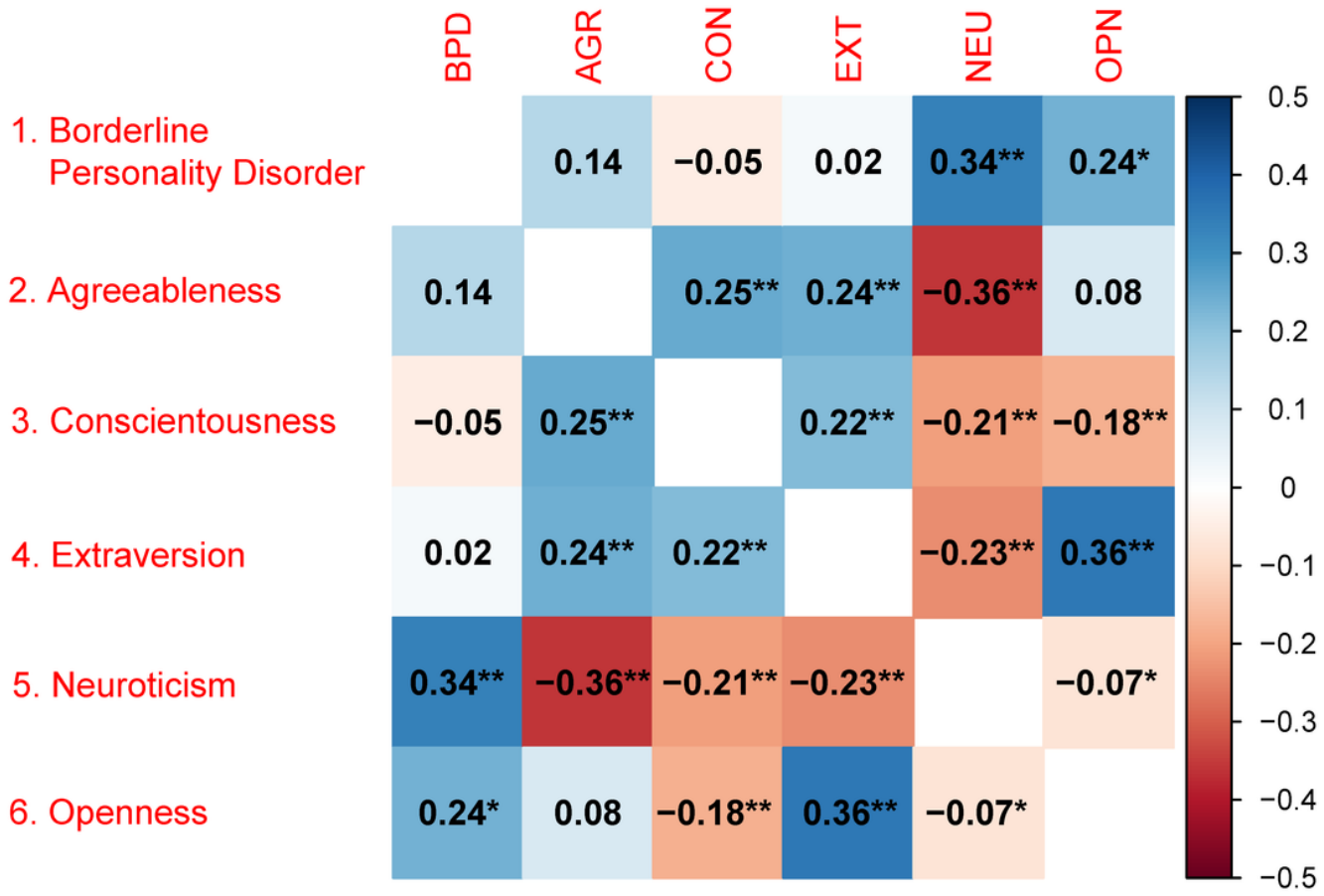

Figure 1

Genetic correlations between Borderline Personality Disorder and the Big Five personality traits Note: Red fields indicate negative and blue fields indicate positive genetic correlations. * $p < 0.05$, ** $p < 0.0033$ (0.05/15 tested correlations). Neuroticism was based on Nagel et al. (Nagel, Jansen, et al. 2018), the other BIG-5 personality traits were based on Lo et al. (2017).

Figure 2

Genetic correlations between Borderline Personality Disorder with clusters and single items of the EPQ-R Neuroticism scale Notes. Colors indicate membership to genetic clusters: red = “Depressed Affect”, green = “Worry”, dark grey = not assigned to a cluster. All data is based on the UK Biobank data sample (Nagel, Jansen, et al. 2018; Nagel, Watanabe, et al. 2018). Within each cluster category, items are sorted by their

genetic correlation with BPD; • p < 0.05, * p < 0.0036 (0.05/14 tested correlations). 95% CI = 95% confidence interval; EPQ-R = Eysenck Personality Questionnaire Revised