Testing Structural Models of Psychopathology at the Genomic Level

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Abstract

Genome-wide association studies (GWAS) have revealed hundreds of genetic loci that underlie major psychiatric disorders, and post-GWAS analyses have discovered substantial genetic correlations among these disorders. This suggests these disorders share a common genetic architecture, implying the presence of a higher-order structure of psychopathology at both the genetic and phenotypic levels. Nonetheless, despite recent efforts at elucidating this structure by collaborative consortia such as HiTOP, the exact structure of psychopathology remains unknown. Herein, in one of the largest genetic studies of psychopathology conducted to date, we tested multiple alternative structural models of psychopathology at the genomic level using the genetic correlations among fourteen psychiatric disorders and related psychological traits estimated from GWAS summary statistics. The best-fitting model includes four correlated higher-order factors - Externalizing, Internalizing, Thought Problems, and Neurodevelopmental Disorders. These higher-order factors were validated by examining their correlations with external criterion variables, which showed distinct patterns of genetic correlations with the 4 higher-order factors. Several model modifications were tested to explore the placement of a few disorders – such as bipolar disorder, OCD, and eating disorders - within the broader psychopathology structure. These findings show support for several of the HiTOP higher-order dimensions and suggest a similar structure of psychopathology at the genomic and phenotypic levels. Our results imply that such higher-order psychopathology dimensions might be better targets for genetic and genomic investigations than individual disorders, and might be more predictive of relevant outcomes of considerable public health and societal concern.

Introduction

Over the past several years, Genome-wide Association Studies (GWAS) have shed considerable light on the causes of major psychiatric disorders, including schizophrenia, bipolar disorder, and depression (1-3). In addition to revealing replicable genetic loci that underlie these disorders, various post-GWAS analyses identify the amount of trait variation that is due to genetic factors (i.e., the single nucleotide polymorphism (SNP)-based heritability) (4,5), as well as the genetic correlations between traits (6). Recent studies have revealed substantial genetic correlations among various psychiatric disorders (6,7), mirroring phenotypic correlations and suggesting shared genetic causes that result from a higher-order structure of psychopathology (8-10).

It has long been accepted that psychopathological traits and disorders are not independent, but are substantially correlated. Researchers have sought to apply models to the observed covariation among these traits, reducing them to their underlying common causes, often referred to as factors (resulting from factor analysis and related psychometric methods). Several alternative models of the underlying phenotypic structure of psychopathology have been advanced in the literature. These include a two-dimensional model in which observed disorders are characterized by Externalizing and Internalizing factors (11), a three-dimensional model that distinguishes Distress from Fears within the Internalizing factor (12), and models that include a Thought Problems factor along with Internalizing and Externalizing factors (13). Recently, researchers have proposed a General factor of psychopathology that influences lower-order symptom dimensions (10,13). One theoretical conceptualization of the structure of psychopathology, the Hierarchical Taxonomy of Psychopathology (HiTOP; 8), posits that general risk for psychopathology is captured by a super spectrum (e.g., a General factor), which in turn influences specific spectra of psychopathology (e.g. Internalizing, Thought Disorder),

which in turn influence increasingly more specific dimensions or subfactors of psychopathology (e.g. fears and distress pathology) and disorders (e.g. major depressive disorder). In practice, the General factor has typically emerged from what is known as a bifactor model. The bifactor model posits that a General factor of psychopathology influences all psychopathology traits and disorders. When particular sets of disorders remain correlated, even in the presence of the overarching general factor, the remaining covariance is modeled by specific factors (e.g. Externalizing and Internalizing) independent of general psychopathology. The General factor of psychopathology and the bifactor model from which it emerges have shown a sharp rise in popularity among psychopathology researchers. Nonetheless, statisticians have pointed out difficulties in distinguishing between bifactor and correlated factor models (14,15) and the tendency for model fit indices to be biased in favor of the bifactor model (16-18). Therefore, the best conceptualization of psychopathology remains an open question.

Some researchers argue that neurogenetic and psychobiological levels of analysis enhance investigation of the structure of psychopathology and augment what is learned through statistical comparisons of behavioral data alone (14). Given this, and the moderate-to-high genetic correlations observed among psychiatric disorders and related psychological traits, examination of the higher-order structure of psychopathology at the genomic level is warranted. Two recent studies have examined the factor structure of psychopathology at the genomic level. Grotzinger and colleagues (19) fit a model that comprised a single common factor of psychopathology using GWAS summary statistics for schizophrenia, bipolar disorder, major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and anxiety disorders. Their results indicated that each disorder had a moderate-to-high loading on the common factor, revealing that genetic covariation among psychiatric disorders can be captured using factor analysis. Lee and colleagues (20) used an exploratory approach to examine the genetic covariance among 8 psychiatric disorders using GWAS summary statistics and found evidence

for a three-factor model which comprised factors representing compulsive behaviors, mood and psychotic disorders, and neurodevelopmental disorders.

In the present study, we employed a systematic approach to compare alternative structural models of psychopathology at the genomic level. We included more disorders and traits than previous studies, capitalizing on the 14 largest GWAS of psychiatric disorders and related psychological traits to obtain estimates of genetic correlations. This study, one of the largest genetic studies of psychopathology conducted to date, tested more alternative models of psychopathology than in previous studies (19,20), guided both by theoretical models in the phenotypic literature and previously estimated genetic correlations. We also evaluated the construct validity of our best-fitting model by estimating genetic correlations between the higher-order factors and relevant traits, such as educational attainment and personality characteristics.

Methods and Materials

GWAS Summary Statistics

Summary statistics for the psychiatric disorders and related traits used in our analyses were drawn from meta-analyses of GWAS with individual-level data. In all, we included in our structural models GWAS results for the 14 disorders and traits listed in Table 1. The GWAS of individual disorders and traits primarily originated from large genetic consortia, including the Psychiatric Genomics Consortium (PGC), The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH; for ADHD and ASD), the Anxiety NeuroGenetics Study (ANGST; for various anxiety disorders), the Tobacco and Genetics Consortium [TGC] for tobacco use, the Early Genetics and Lifecourse Epidemiology [EAGLE] consortium for aggression, and the Broad Antisocial Behavior Consortium [BroadABC] for antisocial behavior. With the exception of schizophrenia and loneliness, for which only GWAS from admixed populations were available, all studies examined individuals from similar ancestral populations (i.e. European descent). Table 1 describes the characteristics of the studies of disorders and

traits included in our analyses. Summary statistics for external criterion traits came from a variety of consortia (i.e., the Social Science Genetic Association Consortium [SSGAC] for the Big 5 personality traits, depression symptoms, subjective wellbeing, educational attainment, age at first birth and number of children; the PGC for loneliness; and the Genetic Investigation of Anthropometric Traits [GIANT] consortium for BMI). Characteristics of studies of the external validity traits are described in Table 2. The total sample size included in analyses was 658,640 participants.

Search and Selection Strategy. A systematic search of repositories of publicly available GWAS summary statistics was conducted to obtain summary statistics from GWAS of psychiatric disorders and related traits and relevant external criterion variables. Summary statistics for ADHD (21), ASD (22), bipolar disorder (3), anorexia (23), MDD (1), OCD (24), schizophrenia (2), PTSD (25), anxiety disorders (26), tobacco use (27), and loneliness (28) were downloaded from the Psychiatric Genomics Consortium (PGC) repository. The summary statistics for antisocial behavior (29) were downloaded from the GWAS Catalog and the summary statistics for aggression (30) were downloaded from the Netherlands Twin Register repository. The summary statistics for age at first birth and number of children (31), neuroticism, subjective wellbeing, depression symptoms (32), and educational attainment (33) were downloaded from the SSGAC repository. Summary statistics for extraversion (34), openness to experience, agreeableness, and conscientiousness (35) were downloaded from the Genetics of Personality Consortium (GPC) repository. Finally, the summary statistics for body mass index (36) were obtained from the GIANT consortium repository. When summary statistics for an existing GWAS could not be found online, the authors of the relevant publication were contacted via email and asked to provide summary statistics, as was the case for alcohol dependence (37) and cannabis dependence (38). When results from more than one GWAS of the same disorder were available, the most recent and largest GWAS was chosen. With the exception of

schizophrenia and loneliness, for which only GWAS from admixed populations were available, we used summary statistics from European ancestry individuals. Tobacco use, antisocial behavior, aggression, and all of the external criterion variables used a continuous variable study design, whereas GWAS for all other psychiatric disorders used a case-control design.

Operationalization of the Phenotypes. For some studies, the operationalization of a case or control was complex, and the criteria used for those phenotypes are described here. Bipolar disorder cases were defined as individuals with one of the following diagnoses: bipolar I, bipolar II, schizoaffective disorder, or another bipolar diagnosis. Anorexia cases required a lifetime diagnosis of anorexia nervosa (either restricting or binge-purging subtypes or lifetime eating disorder not otherwise specified, anorexia nervosa subtype), but a lifetime history of bulimia nervosa was also allowed. These phenotypes were thus described as Eating Disorders (ED) in the Results and Discussion sections below. For the anxiety disorders phenotype, cases were defined as individuals meeting diagnostic criteria for one or more of the following anxiety disorders: generalized anxiety disorder, panic disorder, social phobia, agoraphobia, and specific phobias. Antisocial behavior was operationalized as a continuous phenotype. Measures used by the cohorts in the BroadABC tapped several constructs related to antisocial behavior across a wide age range, including the number of antisocial personality disorder criteria, teacher reports of rule breaking behavior, and parent reports of conduct problems. For PTSD, 87% of controls were trauma exposed but did not go on to develop PTSD, whereas cases were trauma exposed and developed PTSD. Finally, cannabis dependence cases were defined as individuals meeting DSM-IV criteria for cannabis dependence, which included the criterion for withdrawal in some cohorts. Controls were individuals who reported a lifetime history of ever having used cannabis but did not meet criteria for dependence.

Statistical Analysis

All analyses were conducted using the recently developed Genomic Structural Equation Modeling (Genomic-SEM) R package (19). Genomic-SEM employs a novel extension of the widely used Linkage Disequilibrium (LD)-score regression method (4,19) that calculates the genetic covariance among traits using GWAS summary statistics from multiple studies. Briefly, LD is considered the population-level correlation between different genetic markers in the human genome, based on whole-genome sequencing studies. Using the effect estimates of genetic markers on a trait (i.e., GWAS summary statistics) and our estimates of the correlations among genetic markers (i.e., LD scores), Genomic-SEM can obtain estimates of the genetic covariance among numerous traits. Genomic-SEM first estimates a $p \times p$ genetic covariance matrix $\mathbf{S}$ containing genetic heritabilities for each of the *p* disorders or traits on the diagonal and genetic covariances among the *p* disorders and traits in the off-diagonal elements. The estimation uncertainty of $\mathbf{S}$ that is required for accurate structural model estimation is captured in a matrix $\mathbf{V}$, which contains squared standard errors of the estimates in $\mathbf{S}$ on the diagonal, and the covariance between each pair of elements of $\mathbf{S}$ in the off-diagonal. These off-diagonal terms capture the potential sample overlap across traits. After GWAS summary statistics were identified for the 14 psychopathology disorders and traits of interest, the publicly-available summary statistics files were formatted for Genomic-SEM preprocessing (19). Next, the genetic covariance matrix was calculated using LD weights for populations of European ethnicity provided by the Broad Institute and the ldsc() function of the Genomic-SEM R package. The estimated genetic covariance matrix $\mathbf{S}$ and its associated sampling matrix $\mathbf{V}$ were then used for model fitting analyses. Prespecified structural models were fitted and evaluated using the Weighted Least Squares (WLS) discrepancy function. WLS directly incorporates the $\mathbf{V}$ matrix, and is also recommended over maximum likelihood estimation by the creators of Genomic-SEM (19).

Confirmatory Factor Analyses. The alternative *a priori* hypothesized structural models were fitted and compared utilizing confirmatory factor analysis (CFA), which is a form of Structural Equation Modeling (SEM). In a CFA model, correlated observed variables are represented by linear combinations of a smaller number of latent (unobserved) factors that account for the correlations among the observed variables. CFA models provide several parameter estimates within each model, including factor loadings (i.e., weights representing the direction and strength of the relationship between a latent factor and an observed trait) and correlations among the factors. CFA models also provide various indices of how well the overall model fits to the data.

Several models reducing the genetic covariance of the 14 psychopathology traits to hypothesized psychopathology dimensions were fitted in turn. To evaluate the relative performance of each *a priori* hypothesized structural model, we used the Comparative Fit Index (CFI) and the Bayesian Information Criterion (BIC). The fit of each model was evaluated using the combination of CFI and BIC, as each individual fit index has its strengths and limitations and no consensus has been reached regarding the use of a single fit index to evaluate the adequacy of model fit (39). The CFI is an *absolute* index of model fit where values > .90 indicate good fit (40,41), whereas BIC is a *relative* index of model fit that can be used to adjudicate among alternative models (39,42). The model with the lowest value for BIC is considered the best fitting model, and it has been shown that differences of BIC > 10 represent very strong evidence in favor of the model with the lower BIC (43). In addition to these two fit indices, models were considered untenable if they had factor loadings: 1. that were out of bounds (i.e., > |1|), 2. not in the predicted direction (e.g., according to the HiTOP model (8)), 3. not significantly different from zero, or 4. that had very large standard errors. The χ^2 values and degrees of freedom (dfs) are presented in Table 4 for each model tested, but their p values are not used to assess model

fit as models would always be rejected given the very large sample size in our study (39). Instead, the χ^2 values and their dfs were used to calculate the CFI and BIC.

User-defined models were provided to the Genomic SEM software in the lavaan syntax (44). Six CFA models with increasing complexity were specified *a priori* to evaluate and contrast different hypotheses regarding the latent factor structure of psychopathology. The alternative models were defined as follows:

1. **Model 1** included a single, common factor with all traits and disorders loading on that one latent factor.

2. **Model 2** was characterized by three correlated psychopathology factors: Externalizing, Internalizing, and Thought Problems. In this model, Externalizing was indicated by ADHD, aggression, alcohol dependence, cannabis dependence, tobacco use, and antisocial behavior; Internalizing was indicated by MDD, PTSD, anxiety disorders, and eating disorders; and Thought Problems was indicated by schizophrenia, bipolar disorder, OCD, and autism spectrum disorder.

3. **Model 3** included four correlated factors representing Externalizing, Internalizing, Thought Problems, and Substance Use Disorders (SUD). In this model, disorders related to substance abuse (i.e., alcohol dependence, cannabis dependence, and tobacco use) loaded exclusively on the SUD factor rather than on the Externalizing factor (as in Model 2).

4. **Model 4** posited a four-factor structure extending Model 2, in which neurodevelopmental disorders (NDD; ADHD, ASD, and aggression) loaded onto a unique NDD factor. In this model, the NDD disorders were specified with what are known as *cross-loadings:* they were indicators of the same factors from the previous

three-factor model as well as of the NDD factor, which was uncorrelated with the other three factors.

5. **Model 5** was similar to Model 4, except the NDD disorders loaded *only* on the NDD factor, which was correlated with all other factors (Externalizing, Internalizing, Thought Problems).

6. **Model 6** specified a bifactor model with a General Psychopathology factor and four uncorrelated specific factors (Externalizing, Internalizing, Thought Problems, and NDD). In this model all disorders loaded on a General factor as well as on their respective specific factors, which were orthogonal to the General factor and to each other. This structure implies that the correlations among all of the disorders and traits *across* psychopathology domains are due only to the General factor, whereas the correlations among disorders and traits *within* psychopathology domains are also due to the domain-specific factors.

Exploratory Model Modifications. Several exploratory models (labeled Models 5a-5h) were also tested due to conflicting evidence in the psychopathology literature regarding the placement of individual disorders within the overarching multivariate psychopathology structure. All exploratory models were tested as variations of the four-correlated factors model specified in Model 5. First, given the heterogeneous presentation of bipolar disorder (e.g. the potential presence of behavioral dysregulation, depression, and psychotic symptoms), we tested models in which it loaded on Externalizing (Model 5a) and Internalizing (Model 5b) in addition to Thought Problems. Second, because OCD was previously classified in the DSM-IV as part of anxiety disorders and its presentation includes high levels of anxious distress, we next tested models in which OCD loaded on both Thought Problems and Internalizing (Model 5c) and in which it loaded only on Internalizing (Model 5d). Third, given the high genetic correlations between MDD, bipolar disorder and schizophrenia (3), we tested a model in which MDD loaded

on the Thought Problems factor in addition to Internalizing (Model 5e). Fourth, the placement of eating disorders in the multivariate structure of psychopathology is especially unclear as it is not often included in multivariate phenotypic models. Thus, we tested models in which it loaded on Internalizing and Externalizing (Model 5f), on Internalizing and Thought Problems (Model 5g), and on Thought Problems only (Model 5h).

External Validity Analyses. Finally, we sought to validate the higher-order psychopathology factors from the best-fitting model by evaluating their genetic correlations with external criterion traits. Basically, we used additional criterion variables that had also been investigated through GWAS to ensure that our modeled higher-order psychopathology dimensions were correlated with external variables in the expected direction, based on the previous phenotypic literature. For this analysis, we estimated the genetic covariance matrix for all 14 psychopathology disorders and traits plus each of the additional criterion variables. In the Genomic-SEM model, we specified the best-fitting model established previously for the 14 psychopathology disorders and traits of interest, as well as correlations between the higher-order factors and the external criterion variables.

Results

Correlations among Disorders and Traits

Genetic correlations among all 14 disorders and traits are shown in Table 3. Several features of this correlation matrix are noteworthy. First, correlations among disorders were strongest *within* each psychopathology domain (Externalizing, Internalizing, Thought Problems, and Neurodevelopmental Disorders). Second, correlations among disorders *across* psychopathology domains were non-negligible and were in some cases of moderate magnitude, echoing and expanding on recent findings that all psychiatric disorders covary to some extent (6,7).

Model Comparisons

Confirmatory Factor Analyses. Fit statistics of the alternative models reflecting the underlying structure of psychopathology are presented in Table 4. We first contrasted a model with a single common factor (Model 1) with a three-factor model that comprised Externalizing, Internalizing, and Thought Problems dimensions (Model 2). Model 2 had significantly better fit than Model 1, based on a CFI closer to 0.9 and a much smaller BIC (Model 2: χ^2 = 554, df = 74, CFI = .86, BIC = 969.3; Model 1: χ^2 = 1052, df = 77, CFI = .71, BIC = 1427.0; Model 2 vs. Model 1: Δ BIC = 457.7). Next we tested Models 3, 4, and 5, all of which included four factors. Model 3 included Externalizing, Internalizing, Thought Problems and Substance Use Disorders. factors. Model 3 resulted in a larger BIC value than Model 2, indicating that the addition of the SUD factor resulted in a worse-fitting model (Model 3: χ^2 = 548, df = 71, CFI = .86, BIC = 1003.5; Model 2: χ^2 = 554, df = 74, CFI = .86, BIC = 969.3; Model 2 vs. Model 3: Δ BIC = 34.2). In contrast, Model 4 (specifying an NDD factor uncorrelated with EXT, INT, and TP factors) fit better than the three correlated factor model, based on a large reduction in BIC (Model 4: χ^2 = 419, df = 71, CFI = .90, BIC = 874.5; Model 2: χ^2 = 554, df = 74, CFI = .86, BIC = 969.3; Model 4 vs. Model 2: Δ BIC = 94.8). In this model, ADHD, aggression, and ASD loaded on their respective correlated factors in addition to loading on the uncorrelated NDD factor. Model 5, in which the NDD factor was correlated with the other factors, resulted in a CFI above .90 and another substantial reduction in BIC (Model 5: χ^2 = 385, df = 71, CFI = .91, BIC = 840.5; Model 4: χ^2 = 419, df = 71, CFI = .90, BIC = 874.5; Model 5 vs. Model 4: Δ BIC = 34.0). Finally, Model 6 – a bifactor model that comprised a General factor on which all 14 disorders and traits loaded as well the four specific Externalizing, Internalizing, Thought Problems, and Neurodevelopmental Disorders factors, all of which were uncorrelated - fit worse than Model 5 (Model 6: χ^2 = 400, df = 63, CFI = .90, BIC = 962.7 vs. Model 5: χ^2 = 385, df = 71, CFI = .91, BIC = 840.5; Model 5 vs. Model 6: Δ BIC = 122.2). The four correlated factors model (Model 5) thus served as the baseline model for exploring each of the model modifications.

Exploratory Model Modifications. Models in which bipolar disorder loaded on Thought Problems and Externalizing (Model 5a: χ^2 = 384, df = 70, CFI = .91, BIC = 852.9) and Thought Problems and Internalizing (Model 5b: χ^2 = 383, df = 70, CFI = .91, BIC = 851.9) were rejected as they fit slightly worse than the baseline four correlated factors model (Model 5a vs. Model 5: Δ BIC = 12.4; Model 5b vs. Model 5: Δ BIC = 11.4) and due to bipolar disorder's small and negative factor loadings on the Externalizing and Internalizing factors (i.e.,-.01, SE = .10 and -.05, SE = .10). A model in which OCD loaded on Thought Problems and Internalizing (Model 5c: χ^2 = 385, df = 70, CFI = .91, BIC = 853.9) was rejected because it fit slightly worse than the baseline four correlated factors model (Model 5c vs. Model 5: Δ BIC = 13.4) and because OCD had a small and non-significant loading on Internalizing (i.e., .06, SE = .09). Similarly, a model in which OCD loaded only on Internalizing (Model 5d: χ^2 = 402, df = 71, CFI = .90, BIC = 857.5) fit worse than a model in which it loaded only on Thought Problems (Model 5d vs. Model 5, Δ BIC = 17.0). A model in which MDD loaded on Internalizing and Thought Problems (Model 5e: χ^2 = 382, df = 70, CFI = .91, BIC = 850.9) was rejected because it fit slightly worse than the baseline four correlated factors model (Model 5e vs. Model 5: Δ BIC = 10.4) and because MDD had a negative loading on Thought Problems (-.10, SE = .15) and its loading on Internalizing was out of bounds (1.05, SE = .17). Models in which eating disorders loaded on Internalizing and Externalizing (Model 5f) and Internalizing and Thought Problems (Model 5g: χ^2 = 341, df = 70, CFI = .92, BIC = 809.9) were rejected either because they would not run (Model 5f) or due to a negative loading on Internalizing (Model 5g: -.27, SE = .08). However, a model in which eating disorders loaded only on Thought Problems (Model 5h: χ^2 = 341, df = 71, CFI = .92, BIC = 796.5) had a better fit than Model 5 (Model 5h vs. Model 5: Δ BIC = 44.0) and eating disorders loaded most strongly in this model compared to any other model tested. We also tested a bifactor version of this model which fit worse than the best fitting four correlated factors model (χ^2 = 366, df = 63, CFI = .91, BIC = 928.7 vs. Model 5h: χ^2 = 341, df = 71, CFI = .92,

BIC = 796.5; Δ BIC = 132.2). There also were several issues with the bifactor model that led us to reject it. Specifically, as shown in Table 5, all of the disorders' loadings on the Externalizing and Internalizing specific factors became nonsignificant and some loadings became negative (cannabis and PTSD) after accounting for their loading on the General factor, while the loading of eating disorders on the General factor was negative and nonsignificant. In addition, many of the factor loadings' standard errors were much larger than in the four correlated factors model.

Our results thus suggest that the best-fitting model comprises four moderately correlated factors of Externalizing, Internalizing, Thought Problems, and Neurodevelopmental Disorders in which eating disorders loads only on Thought Problems (Model 5h). As shown in Figure 1 and Table 5, all factor loadings and correlations were significant, as they were greater than twice their standard errors, and were moderate to high with the exception of eating disorders (ED), which had a small but significant loading on Thought Problems. The average of the disorders' and traits' genetic variance accounted for by the factors was substantial (Internalizing = .54, Externalizing = .33, Thought Problems = .38, and Neurodevelopmental Disorders = .49).

The Externalizing and Internalizing factors were positively and moderately correlated with all other factors and with each other, while Thought Problems and NDD were only weakly correlated. As shown in Figure 1, the NDD factor was moderately to highly genetically correlated with the Externalizing and Internalizing factors (r_g's = .67 and .75, respectively), suggesting that the genes that predispose to Neurodevelopmental Disorders in early childhood also predispose to Externalizing and Internalizing disorders later in childhood and in adolescence.

External Validity Analyses. Figure 2 presents the differential genetic correlations between the higher-order psychopathology dimensions from Model 5h and the external criterion variables listed in Table 2. The Externalizing factor was more strongly correlated with extraversion, age at first birth (negative), and educational attainment (negative) than were the

Internalizing and NDD factors. The Thought Problems dimension had the weakest correlations with these external variables. The Externalizing and NDD dimensions were more strongly correlated with total number of children born than were the Internalizing or Thought Problems dimensions. In contrast, the Internalizing factor was strongly related to loneliness, depression symptoms, subjective wellbeing (negative), and neuroticism, as would be expected based on the previous phenotypic literature and the conceptualization of Internalizing psychopathology. The Externalizing and NDD factors were more strongly associated with these criteria than Thought Problems. Externalizing, Internalizing, and NDD had similar negative associations with Conscientiousness, Agreeableness, and BMI. Finally, Thought Problems was positively correlated with Openness to Experience and educational attainment, whereas the other factors were either unrelated or negatively related. Most crucially, the direction of associations between the four higher-order psychopathology factors and the external criteria were in the expected direction, and the relative magnitude of the four factors' genetic correlations with the external criteria also matched theoretical expectations. For example, all psychopathology dimensions had some association with loneliness, depressive symptoms, and subjective well-being, but the Internalizing factor displayed the largest associations. This is intuitive, given that a GWAS of MDD was one of the original disorders that informed the Internalizing dimension. These different patterns of genetic correlations provide evidence for the external validity of the higher-order psychopathology factors.

Discussion

Herein, factor analyses of GWAS summary statistics for 14 psychiatric disorders and related traits revealed four moderately correlated factors - Externalizing, Internalizing, Thought Problems, and Neurodevelopmental Disorders - which showed distinct and expected patterns of genetic correlations with external validity variables. A bifactor model composed of a General factor of psychopathology did not fit as well as the corresponding best-fitting correlated factors model and yielded problematic model characteristics, suggestive of overfitting. Given that our

analyses used GWAS summary statistics from 14 different studies, it is noteworthy that our best-fitting model mirrored features found in many phenotypic factor analyses, such as moderate to high factor loadings and moderate factor correlations. Indeed, these features and the four factors in our best-fitting model mirror crucial aspects of the HiTOP model of psychopathology. In addition, each GWAS comprises meta-analyses of distinct cohorts, rather than a single cohort in which participants reported on all disorders simultaneously. Our analyses are thus unaffected by issues such as shared measurement error, response biases, common method variance, and smaller sample size that can affect phenotypic studies. It is worth noting that many of the models we tested fell short of conventional standards for good model fit, likely due to the limitations of extant GWAS summary statistics, although the best fitting model did surpass standards for good fit (i.e., CFI > .90). The four factors were also differentially associated with external criterion variables, suggesting that the factors represent meaningfully distinct dimensions of psychopathology. Further, the direction and magnitude of these correlations is consistent with previous phenotypic (45,46) and genetic studies (32,47-49) of the nomological network of higher-order dimensions of psychopathology. Finally, the NDD factor was moderately to highly genetically correlated with the Externalizing and Internalizing factors, suggesting that the genes that predispose to Neurodevelopmental Disorders in early childhood also predispose to Externalizing and Internalizing disorders later in childhood and in adolescence. This suggests an etiological basis for the association of ADHD or ASD in childhood with antisocial behavior, substance use disorders, anxiety, and depression in adolescence and adulthood.

Two previous studies have modeled the structure of psychopathology using GWAS summary statistics (19,20) and our results strengthen the main conclusion of these studies that factor analysis can be used to model genetic covariation among psychopathological disorders. The current study adds to this literature by including a greater number of psychiatric disorders and related psychological traits in the analyses and testing a greater number of alternative

models of psychopathology. The best-fitting model in the current study indicated that eating disorders and OCD, on the one hand, and bipolar disorder and schizophrenia, on the other, load together on the same Thought Problems factor, which mirrors findings from a previous study (19). We also replicated the finding that ASD and ADHD load together on a separate Neurodevelopmental Disorders factor (20). Nevertheless, our results differ from these two previous studies in a number of important ways. First, using Confirmatory Factor Analyses, we found that the fourteen disorders and related traits included in our study were best represented by four correlated factors, including a Thought Problems factor onto which bipolar disorder, schizophrenia, OCD, and eating disorders loaded. Second, our findings suggest that MDD loads together with other Internalizing disorders rather than with bipolar disorder and schizophrenia. These differences in results across studies illustrate how the inclusion or exclusion of particular disorders or traits, as well as the use of different statistical methods, can yield different results.

For disorders whose placement in the multivariate higher-order structure of psychopathology is still up for debate, we tested alternative models in which the disorder loaded on multiple factors. The most notable such modification is the placement of eating disorders, which ultimately loaded on the Thought Problems factor. The relative placement of eating disorders within the higher-order structure of psychopathology has been debated. Most recently, structural models of psychopathology suggest that it can be placed within the Internalizing framework (50,51), although some models suggest it is a separate dimension (8). However, in the current analyses, eating disorders loaded most strongly on the Thought Problems factor, perhaps suggesting that this factor is characterized by disturbed cognitions found across disparate psychopathological disorders. The placement of eating disorders on this factor is also consistent with previous studies that have found substantial covariation between eating disorders and OCD (52,53), which also loaded on the Thought Problems factor in the current study.

Our findings can also be contextualized within the current literature on the phenotypic structure of psychopathology. The HiTOP model, which posits that general risk for psychopathology is reflected by a super spectrum (e.g. a General factor) which influences lower-order spectra (e.g. internalizing, through disorder), which in turn influence increasingly specific subfactors (e.g. eating pathology) and disorders (e.g. major depressive disorder), is one such framework (8). Importantly, this model includes most forms of psychopathology, many of which have not been studied in a GWAS and were thus not included in the current analyses. However, comparison of our results with the HiTOP model yields several interesting points. First, the HiTOP model, and indeed other phenotypic models of psychopathology (54,55), distinguish between disinhibited (e.g. substance use) and antagonistic (e.g. antisocial personality and other personality disorders) forms of Externalizing. In our analyses, however, a model that distinguished substance use pathology from other externalizing disorders did not perform well. Second, in the HiTOP framework, eating disorders and OCD are clustered within internalizing psychopathology, whereas they were best characterized within the Thought Problems factor in the current study. The relative placement of OCD and eating disorders within the higher-order genetic models may change as GWAS for more specific internalizing disorders become available. Finally, the HiTOP model tentatively posits that mania can be captured within both internalizing and thought disorder factors; however, our inability to distinguish between mania and depression within bipolar disorder precluded a test of this model. Rather, bipolar disorder loaded with other thought disorders, perhaps reflecting the strong genetic relationship between more severe mania and schizophrenia (3). As GWAS summary statistics become available on more fine-grained dimensions of psychopathology we will be able to test more detailed models posited within the HiTOP framework, such as distinguishing between fears and distress pathology within internalizing and modeling dimensions of detachment and somatoform psychopathology.

Modeling higher-order psychopathology dimensions may have several advantages for genetic studies over studying individual diagnoses one at a time. These include a more parsimonious and accurate representation of psychopathology (8), higher heritability, capitalization on pleiotropy to increase genetic associations (56,57), greater genetic correlations with external variables, greater statistical power to detect genetic associations due to more information contained in latent continuous versus observed categorical phenotypes (54,55), and elimination of measurement error. These advantages, as well as GWAS of more fine-grained phenotypes (e.g., of distinct anxiety disorders), should increase the genetic signal and consequently the number of genome-wide significant associations found in GWAS (58). The resolving power of such factor analyses should only increase as individual GWAS meta-analyses become larger and better powered statistically, and as continuous psychopathology dimensions are included as phenotypes in GWAS, both of which should result in higher GWAS-based heritabilities and greater genetic signal to model. Future studies using GWAS of continuous psychopathology dimensions in large samples should attempt to replicate the higher-order structure of psychopathology presented herein.

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Table 1. Characteristics of Studies of Disorders and Traits Included in Analyses

Phenotype	Study	Year	Data Source	Sample Size (cases/ controls)	Sample/Pop Prevalence	Study Design	Effect Size	Ancestry
ADHD	DeMontis et al.	2017	PGC-iPSYCH	20,183/ 35,191	.36/ .11[1]	Case-control	OR	European
Alcohol Dependence	Walters et al.	2018	PGC	10,206/ 28,480	.26/ .12[2]	Case-control	OR	European
Cannabis Dependence	Agrawal et al.	2018	PGC	3,757/ 9,931	.26/ .02[3]	Case-control	Beta	European
Tobacco Use	Furberg et al.	2010	TGC	73,853	NA/ NA	Continuous	Beta	European
Aggression	Pappa et al.	2016	EAGLE	18,988	NA/ NA	Continuous	Beta	European
Antisocial Behavior	Tielbeek et al.	2017	BroadABC	16,400	NA/ NA	Continuous	Beta	European
Eating Disorders	Duncan et al.	2017	PGC	3,495/ 10,982	.17/.02[1]	Case-control	OR	European
Anxiety Disorders	Otowa et al.	2016	ANGST/PGC	7,016/ 14,745	.32/ .19[1]	Case-control	Beta	European
PTSD	Duncan et al.	2017	PGC	2,424/ 7,113	.25/ .07[1]	Case-control	OR	European
MDD	Wray et al.	2018	PGC-iPSYCH	59,851/ 113,154	.35/ .07[1]	Case-control	OR	European
OCD	Arnold et al.	2017	IOCDF-OCGWAS	2,688/ 7,037	.28/ .02[1]	Case-control	OR	European
Schizophrenia	Ripke et al.	2014	PGC	36,989/ 113,075	.25/ .01[1]	Case-control	OR	Admixed
Bipolar Disorder	Stahl et al.	2019	PGC	20,352/31,358	.39/ .01[1]	Case-control	OR	European
ASD	Grove et al.	2019	PGC-iPSYCH	18,382/ 27,969	.40/ .02[1]	Case-control	OR	European

Note. ADHD = attention deficit hyperactivity disorder, PTSD = post traumatic stress disorder, MDD = major depressive disorder, OCD = obsessive compulsive disorder, ASD = autism spectrum disorder, PGC = Psychiatric Genetics Consortium, iPsych = The Lundbeck Foundation Initiative for Integrative Psychiatric Research, EAGLE = Early Genetics and Life Course Epidemiology, BroadABC = Broad Antisocial Behavior Consortium, ANGST/PGC = Anxiety NeuroGenetics Study, IOCDF = International Obsessive Compulsive Disorder Foundation Genetics Collaborative, OCGAS = OCD Collaborative Genetics Association Studies, TGC = Tobacco and Genetics Consortium, NA = Not reported by the authors, OR = Odds Ratio, Beta = Standardized regression coefficient.

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Table 2. Characteristics of External Validity Variables

Phenotype	Study	Year	Data Source	Sample Size	Study Design	Effect Size	Ancestry
Neuroticism	Okbay et al.	2016	SSGAC	298,420	Continuous	Beta	European
Depression Symptoms	Okbay et al.	2016	SSGAC	161,460	Continuous	Beta	European
Subjective Wellbeing	Okbay et al.	2016	SSGAC	298,420	Continuous	Beta	European
Extraversion	Van Den Berg et al.	2015	GPC	170,910	Continuous	Beta	European
Agreeableness	De Moor et al.	2012	GPC	20,669	Continuous	Beta	European
Conscientiousness	De Moor et al.	2012	GPC	20,669	Continuous	Beta	European
Openness	De Moor et al.	2012	GPC	20,669	Continuous	Beta	European
Educational Attainment	Lee et al.	2018	SSGAC	766,345	Continuous	Beta	European
Loneliness	Gao et al.	2016	PGC	10,760	Continuous	Beta	Admixed
Body Mass Index	Yengo et al.	2018	GIANT + UK Biobank	681,275	Continuous	Beta	European
Number of Children	Barban et al.	2016	SSGAC	333,702	Continuous	Beta	European
Age at First Birth	Barban et al.	2016	SSGAC	237,516	Continuous	Beta	European

Note: SSGAC = Social Science Genetic Association Consortium, GPC = Genetics of Personality Consortium, PGC = Psychiatric Genetics Consortium, GIANT = Genetic Investigation of Anthropometric Traits consortium, Beta = Standardized regression coefficient.

Table 3. Genetic correlations among the 14 psychiatric disorders and related traits

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. AGG	1													
2. ADHD	0.77	1												
3. ASD	0.49	0.37	1											
4. CIGS	0.52	0.41	0.07	1										
5. CAN	0.81	0.42	0.03	0.12	1									
6. ALC	0.12	0.41	0.02	0.33	0.12	1								
7. ASB	0.24	0.52	0.21	0.20	0.41	0.59	1							
8. ANX	0.67	0.30	0.28	0.09	0.35	0.54	0.42	1						
9. MDD	0.46	0.56	0.44	0.16	0.23	0.44	0.55	0.89	1					
10. PTSD	0.40	0.52	0.24	0.44	0.41	0.33	0.36	0.09	0.49	1				
11. BIP	0.11	0.12	0.13	0.20	0.34	0.24	0.11	0.18	0.33	0.07	1			
12. OCD	0.38	-0.16	0.12	-0.05	0.25	-0.27	-0.05	0.30	0.30	0.42	0.32	1		
13. SCZ	0.04	0.12	0.21	0.11	0.07	0.09	0.09	0.26	0.37	0.18	0.68	0.33	1	
14. ED	-0.20	-0.26	-0.08	-0.12	0.04	-0.10	-0.10	0.09	0.20	-.02	0.18	0.50	0.23	1

Note. AGG = aggression, ADHD = attention/deficit-hyperactivity disorder, ASD = autism spectrum disorder, CIGS = number of cigarettes smoked per day, CAN = cannabis dependence, ALC = alcohol dependence, ASB = antisocial behavior, ANX = anxiety disorders, MDD = major depressive disorder, PTSD = post-traumatic stress disorders, BIP = bipolar disorder, OCD = obsessive compulsive disorder, SCZ = schizophrenia, ED = eating disorders. Borders denote correlations among disorders within each higher-order dimension.

Table 4. Models and Model Fit Statistics

Model	χ^2	df	CFI	BIC	Model Compared to	ΔBIC
1. One common factor	1052	77	0.71	1427.0		
2. Three correlated factors (EXT, INT, and TP)	554	74	0.86	969.3	1	457.7
3. Four correlated factors (EXT, INT, TP, and SUD)	548	71	0.86	1003.5	2	+ 34.2
4. Four factor model (EXT, INT, TP, and uncorrelated NDD)	419	71	0.90	874.5	2	94.8
5. Four correlated factors (EXT, INT, TP, and NDD, ED on INT)	385	71	0.91	840.5	4	34.0
6. Bifactor model, with four uncorrelated specific factors (ED on INT only)	400	63	0.90	962.7	5	+122.2
Modified four correlated factors models						
5a. Four correlated factors, BIP on TP and EXT	384	70	0.91	852.9	5	12.4
5b. Four correlated factors, BIP on TP and INT	383	70	0.91	851.9	5	11.4
5c. Four correlated factors, OCD on TP and INT	385	70	0.91	853.9	5	13.4
5d. Four correlated factors, OCD on INT only	402	71	0.90	857.5	5	17.0
5e. Four correlated factors, MDD on INT and TP	382	70	0.91	850.9	5	10.4
5f. Four correlated factors, ED on INT and EXT	MODEL WOULD NOT RUN					
5g. Four correlated factors, ED on INT and TP	341	70	0.92	809.9	5	30.6
5h. Four correlated factors, ED on TP only	**341**	**71**	**0.92**	**796.5**	**5**	**44.0**
5i. Bifactor model, with four uncorrelated specific factors (ED on TP only)	366	63	0.91	928.7	5h	+ 132.2

Note. BIC = Bayesian Information Criterion, EXT = Externalizing factor, INT = Internalizing factor, TP = Thought Problems factor, SUD = Substance Use Disorders factor, NDD = Neurodevelopmental Disorders factor, BIP = bipolar disorder, OCD = obsessive compulsive disorder, MDD = major depressive disorder, ED = eating disorders.df = degrees of freedom, CFI = Comparative Fit Index, BIC = Bayesian Information Criterion. The model in bold is the best-fitting model based on a BIC difference > 10. Δ BICs that have plus signs indicate that the more parsimonious models have better fit than the more complex models.

Table 5. Standardized Factor Loadings and Factor Correlations from the Modified Correlated Factors Model and its Corresponding Bifactor Model

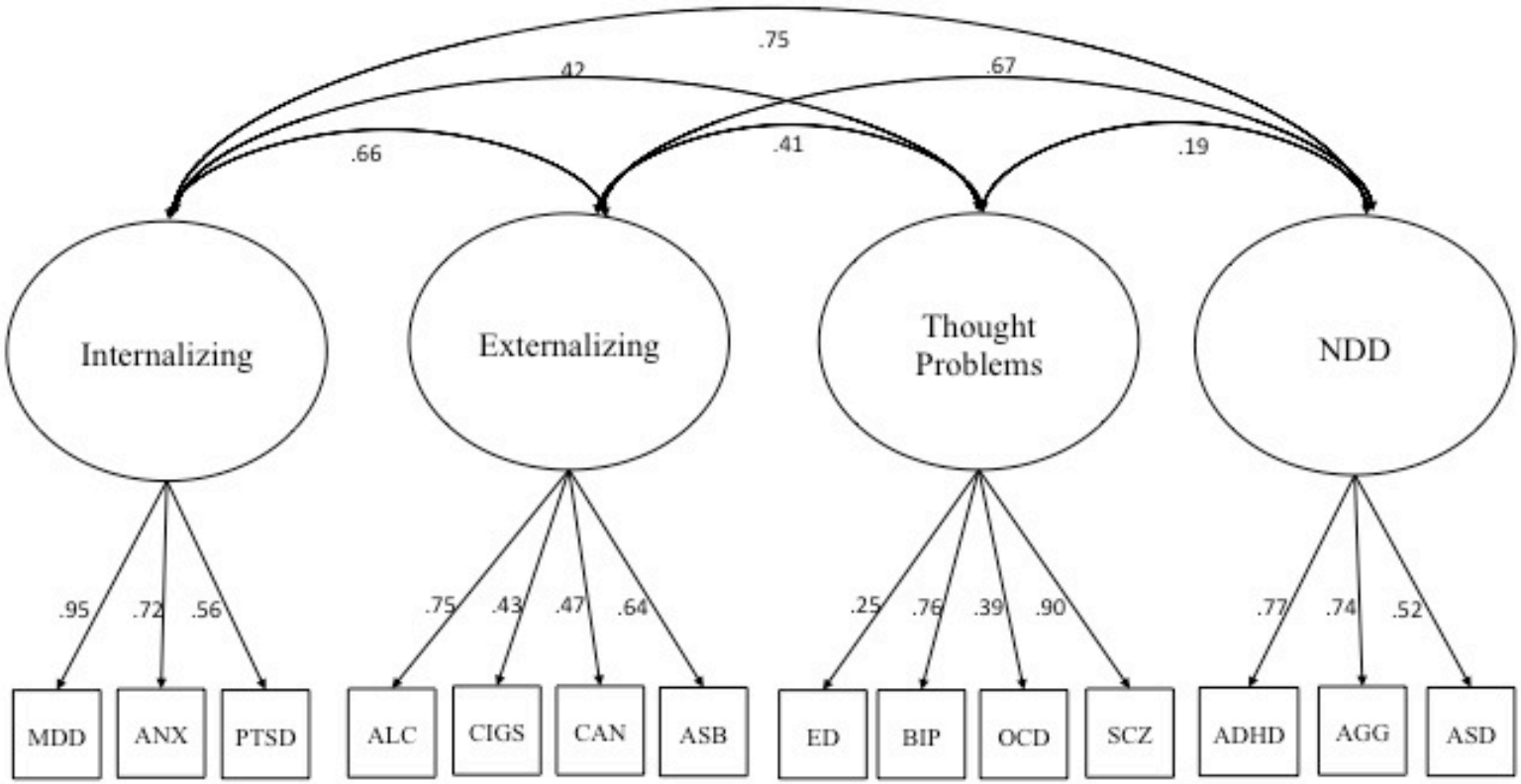
Disorder/Trait	Four Correlated Factors Model (Model 5h) β (SE)				Bifactor Model with Four Specific Factors (Model 5i) β (SE)				
	EXT	INT	TP	NDD	GEN	EXT	INT	TP	NDD
Antisocial Behavior	.64 (.14)***				.55 (.10)***	.29 (.75)			
Tobacco	.43 (.09)***				.34 (.07)***	.15 (.40)			
Alcohol	.75 (.13)***				.60 (.06)***	.80 (2.01)			
Cannabis	.47 (.16)**				.41 (.13)**	-.10 (.43)			
PTSD		.56 (.09)***			.68 (.15)***		-.69 (.68)		
MDD		.95 (.10)***			.94 (.08)***		.31 (.25)		
Anxiety		.72 (.09)***			.67 (.12)***		.50 (.33)		
Eating Disorder			.25 (.05)***		-.05 (.06)			.32 (.06)***	
Schizophrenia			.90 (.05)***		.36 (.03)***			.78 (.08)***	
Bipolar Disorder			.76 (.04)***		.30 (.03)***			.73 (.08)***	
OCD			.39 (.05)***		.15 (.07)*			.38 (.07)***	
ASD				.52 (.05)***	.41 (.05)***				.29 (.12)*
Aggression				.74 (.12)***	.44 (.12)***				.86 (.36)*
ADHD				.77 (.06)***	.54 (.05)***				.50 (.21)*
EXT	–				–	–	–	–	–
INT	.66 (.14)***	–			–	–	–	–	–
TP	.41 (.08)***	.42 (.05)***	–		–	–	–	–	–
NDD	.67 (.15)***	.75 (.09)***	.19 (.04)***	–	–	–	–	–	–

Note. ADHD = attention/deficit-hyperactivity disorder, ASD = autism spectrum disorder, MDD = major depressive disorder, PTSD = post-traumatic stress disorders, OCD = obsessive compulsive disorder, EXT = Externalizing factor, INT = Internalizing factor, TP = Thought Problems factor, NDD = Neurodevelopmental Disorders factor, GEN = General factor, β = Standardized regression coefficient, SE = Standard Error. * p < .05, ** p < .01, *** p < .001.

Figure 1. Best-Fitting CFA Model
Note. NDD = Neurodevelopmental Disorders, SCZ = schizophrenia, OCD = obsessive compulsive disorder, BIP = bipolar disorder, ASD = autism spectrum disorder, PTSD = post-traumatic stress disorder, MDD = major depressive disorder, ANX = anxiety disorders, ED = eating disorders, ASB = antisocial behavior, ALC = alcohol dependence, CAN = cannabis dependence, CIGS = number of cigarettes smoked per day, ADHD = attention/deficit-hyperactivity disorder, AGG = aggression.

Figure 2. Genetic Correlations of the External Validity Variables with the Four Higher-Order Psychopathology Factors
Note. EXT = Externalizing higher-order factor, INT = Internalizing higher-order factor, TP = Thought Problems higher-order factor, NDD = Neurodevelopmental Disorders higher-order factor, Error bars are 95% confidence intervals.

Figure 1.


.75
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Internalizing
Externalizing
Thought Problems
NDD
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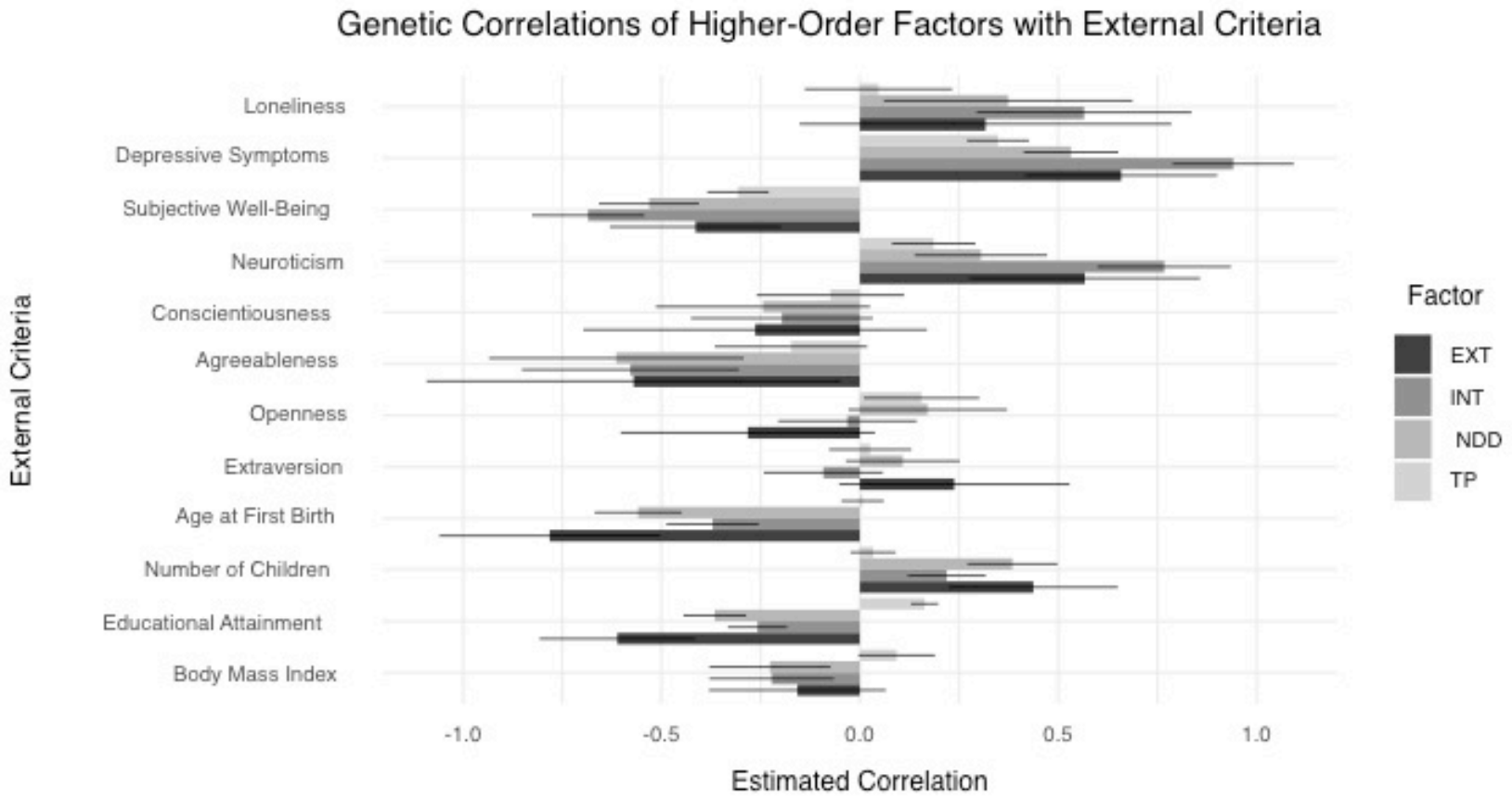
MDD
ANX
PTSD
ALC
CIGS
CAN
ASB
ED
BIP
OCD
SCZ
ADHD
AGG
ASD

Figure 2.


Genetic Correlations of Higher-Order Factors with External Criteria
External Criteria
Loneliness
Depressive Symptoms
Subjective Well-Being
Neuroticism
Conscientiousness
Agreeableness
Openness
Extraversion
Age at First Birth
Number of Children
Educational Attainment
Body Mass Index
-1.0
-0.5
0.0
0.5
1.0
Estimated Correlation
Factor
EXT
INT
NDD
TP