Testing Structural Models of Psychopathology at the Genomic Level

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Summary

Recent Genome-wide Association Studies (GWAS) have revealed hundreds of genetic loci that underlie major psychiatric disorders[1-3]. Post-GWAS analyses have also revealed substantial genetic correlations among various psychiatric disorders[4,5]. This suggests these disorders share common genetic causes, implying the presence of a higher-order structure of psychopathology[6-8]. In this paper, we test multiple structural models of psychopathology at the genomic level using the genetic correlations among fourteen psychiatric disorders and related traits. We show that the best-fitting model contains three correlated factors - Externalizing, Internalizing, and Thought Problems – and an uncorrelated Neurodevelopmental Disorders factor, but no General Psychopathology factor. These factors show distinct patterns of genetic correlations with relevant traits and account for substantial genetic variance in their constituent disorders. These findings also suggest a similar structure of psychopathology at the genomic and phenotypic levels[9]. Such higher-order psychopathology factors are potentially better targets for GWAS than individual disorders and more predictive of external criterion variables.

Over the past few 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 estimate the magnitude of genetic variation underlying a trait or disorder due to genetic variants (i.e., SNP-based heritability)[10,11], as well as the genetic correlation between traits or disorders[4]. Recently, studies using such methods have revealed substantial genetic correlations among various psychiatric disorders[4,5], mirroring phenotypic correlations among these disorders, and suggesting these disorders have shared genetic causes which give rise to a higher-order structure of psychopathology[6-8].

Various models of the underlying phenotypic structure of psychopathology have been advanced in the psychopathology literature. These have included a two-factor model comprising Externalizing and Internalizing dimensions[12], a three factor model that distinguishes Distress from Fears within Internalizing[13], and models that also include a Thought Problems factor[9]. Recently, researchers have proposed a General factor of psychopathology that influences lower-order symptom dimensions[8,9]. This General factor has emerged from a bifactor model that includes the General factor which influences all disorders and the aforementioned other dimensions as specific factors that influence a subset of disorders and are uncorrelated with the General factor. The General factor of psychopathology and the bifactor model from which it emerges have shown a sharp rise in usage and popularity among psychopathology researchers. Nonetheless, statisticians have pointed out difficulties in distinguishing between bifactor and correlated factor models[14,15] and the tendency for common model

fit indices to be biased in favor of the bifactor model[16,17]. These researchers argue that neurogenetic and psychobiological levels of analysis are more valuable than pure statistical comparison for investigating the structure of psychopathology[14]. Consequently, in this paper we use the genetic correlations among 14 psychiatric disorders and related traits to test alternative structural models of psychopathology at the genomic level.

Results

The heritabilities of and genetic correlations among disorders

We analyzed GWAS summary statistics using *Genomic Structural Equation Modeling* (Genomic-SEM)[18] which uses multivariate LD-score regression to estimate the heritabilities of and genetic correlations among each disorder / trait, as well as to test the alternative structural models of psychopathology. A brief description of the characteristics of each dataset included in the analyses, as well as the heritability of each disorder presented in the original GWAS publication and estimated by Genomic-SEM, is shown in Supplemental Table 1. As shown in the Table, with the exception of schizophrenia, the heritability of each disorder as estimated by the Genomic-SEM program is highly similar to that in the original study. Correlations among the 14 disorders / traits are shown in the heatmap in Figure 1. Several features of this correlation matrix are noteworthy. First, correlations among disorders are strongest within each psychopathology domain (Externalizing, Internalizing, and Thought Problems), as can be seen by the demarcations using the dashed lines. Second, correlations among disorders across psychopathology domains are non-negligible and

are at times of moderate magnitude, echoing and expanding on recent previous findings[4,5].

Testing alternative models of the structure of psychopathology

Models specifying the alternative underlying structures of psychopathology are presented in Table 1. We used Confirmatory Factor Analyses (CFAs) - implemented in Genomic-SEM[18] - and a combination of model fit and model characteristics to adjudicate among the alternative structural models of psychopathology. Specifically, better fitting models were characterized by a higher Comparative Fit Index (CFI), lower Bayesian Information Criterion (BIC), and lower Root Mean Square Residuals (RMSR) [18]. Model characteristics that were deemed problematic were factor loadings that were out of bounds (I.e., > |1|), negative, or very low (relative to their standard errors) and not significantly different from zero, as well as very large standard errors for those factor loadings.

We tested the alternative models in a sequential fashion. Our results suggest the best fitting model comprises three moderately correlated factors of Externalizing, Internalizing, and Thought Problems, as well as an independent Neurodevelopmental Disorders factor. As shown in Figures 2 and 3, all factor loadings were moderate to high with the exception of Eating Disorders (ED) on Internalizing, and the factor correlations were moderate. All factor loadings and correlations were significant, as their 95% confidence intervals did not include zero (shown in Supplemental Table 2). The average of the disorders' and traits' genetic variance accounted for by the factors (Internalizing = .46, Externalizing = .36, Thought Problems = .42, and

Neurodevelopmental Disorders = .36) was also much greater than the heritability of each of the constituent disorders and traits.

As shown in Table 1 and Figure 2, a model with three correlated Externalizing, Internalizing, and Thought Problems factors fit better than a model with a single General Psychopathology factor (Model 2 versus Model 1). A bifactor model that included the three correlated factors as well as a General factor fit much worse (Model 3). Similarly, a model that distinguished a substance use disorder factor from the other Externalizing disorders and traits (i.e., ADHD, Aggression, and Antisocial Behavior) fit worse (Model 4). A best-fitting model (shown in Figure 3 and in Supplemental Table 2) that distinguished an uncorrelated Neurodevelopmental Disorders factor (that included ADHD, ASD, and aggression) from the other adult psychopathology disorders fit even better (Model 5), as did a model in which these symptom dimensions only loaded on a correlated Neurodevelopmental Disorders factor (Model 6). Other alternative structural models did not fit as well. Models in which Bipolar Disorder loaded on Externalizing and Internalizing (Model 7 and 8), and OCD loaded on Internalizing (Model 9), in addition to their both loading on Thought Problems fit better but were rejected given that the factor loadings were small or in the wrong direction. A model in which Eating Disorders loaded on Externalizing as well as Internalizing (Model 10) fit better but was rejected because the factor loadings were out of bounds and their standard errors increased dramatically. Finally, although a modified bifactor model (Model 11) fit well, it required constraining all of the residual variances to be greater than zero and yielded problematic standard errors, both indicators of overfitting (as shown in Supplemental Table 3).

Associations of the higher-order psychopathology factors with relevant correlates

The higher-order psychopathology factors differed in their associations with external criterion variables (described in Supplementary Table 4), as shown in Figure 4 and Supplemental Figure 1. Externalizing was more related to Agreeableness, Conscientiousness, age at first birth, the number of live births, BMI, and Educational Attainment than was Internalizing, which was more related to these variables than was Thought Problems. Externalizing was also positively related to Extraversion, whereas Internalizing was negatively related and Thought Problems was unrelated. In contrast, Internalizing was more related to Neuroticism, Loneliness, Subjective Well-Being, and Depression than was Externalizing, which was more related to these variables than was Thought Problems. Finally, Thought Problems was positively related to Openness to Experience, BMI, and Educational Attainment, whereas Internalizing and Externalizing were unrelated or negatively related. 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 three moderately correlated Externalizing, Internalizing, and Thought Problems factors, and an orthogonal Neurodevelopmental Disorders factor, which showed distinct patterns of association with external validity variables. A bifactor model containing a General factor fit extremely poorly, and yielded problematic model characteristics even when constraints were imposed on the model to improve fit,

suggesting overfitting. 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, given that our analyses used GWAS summary statistics from 14 different studies - each comprising meta-analyses of many distinct samples - rather than a single sample 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[19]. It is worth noting, however, that even the best-fitting model fell short of conventional standards for acceptable model fit, likely due to the limitations of extant GWAS summary statistics.

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[6], higher heritability, capitalization on pleiotropy to increase genetic associations[19,20], 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[21], and elimination of measurement error[22]. 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 in GWAS. 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 SNP-based heritabilities and greater genetic signal to model.

Method

GWAS Summary Statistics

Summary statistics for psychiatric disorders used in analyses were drawn from meta-analyses of GWAS run on individual samples, generated mainly by the PGC. In some cases, these samples were augmented by samples from other consortia, like iPSYCH or ANGST (for ADHD, MDD, Anxiety Disorder, and ASD). In other cases, the summary statistics were generated by other sources (i.e., the Tobacco and Genetics Consortium for tobacco use, the EAGLE consortium for aggression, and the BroadABC consortium for antisocial behavior). Summary statistics for external criterion variables came from a variety of consortia (i.e., the SSGAC for the Big 5 personality traits[23-25], depression symptoms[25], subjective wellbeing[25], and Educational Attainment[26]; the UK Biobank for age at first birth and number of children, PGC for loneliness[27], and GIANT for BMI[28]).

A systematic search of repositories of publicly available GWAS summary statistics was conducted to obtain summary statistics from GWAS of psychiatric disorders and relevant external criterion variables. Summary statistics for ADHD[29], ASD[30], bipolar disorder[3], anorexia[31], MDD[2], OCD[32], schizophrenia[1], PTSD[33], anxiety disorders[34], tobacco use[35], and loneliness[27] were downloaded from the Psychiatric Genomics Consortiums repository. The summary statistics for antisocial behavior[36] were downloaded from the GWAS Catalog and the summary statistics for aggression[37] were downloaded from the Netherlands Twin Register repository. The summary statistics from the SSGAC, PGC and GIANT were downloaded from the respective

associations' websites. GWAS summary statistics for UK Biobank traits were obtained from the public release updated in August 2018 on http://www.nealelab.is/uk-biobank/. 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 (for alcohol dependence[38] and cannabis dependence[39]). When results from more than one GWAS of the same disorder were available, the most recent, and largest, GWAS was chosen. We used summary statistics from European ancestry individuals except for the studies of schizophrenia and loneliness, for which only GWAS from admixed populations were available. With the exception of tobacco use, antisocial behavior, aggression, and the external criterion variables, all studies used a case-control design.

For some studies, the operationalization of a case or control was complex, and the criteria used for those phenotypes are described here. Bipolar 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. 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 modeled 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, cases were individuals with trauma exposure who went on to develop PTSD while most controls were individuals who were trauma exposed but did not meet criteria for PTSD. Finally, cannabis dependence cases were defined as individuals meeting DSM-IV criteria for cannabis dependence, which included withdrawal in some cohorts. Controls were individuals who reported a lifetime history of ever having used cannabis but did not meet criteria for dependence.

When possible, the following data were extracted from each article corresponding to the summary statistics obtained in the steps above: authors, year of publication, journal in which the study was published, title of article, sample size, phenotype assessed, sample prevalence (i.e. percentage of affected individuals) in case-control studies, cohorts included in the study, study design, ancestry of genotyped individuals, metric of effect size (e.g. Beta, Odds Ratio, etc), and published SNP-based heritability. With the exception of alcohol and cannabis dependence, the population prevalence of each disorder in a case-control study was obtained from the National Institute of Mental Health online statistics page[40]. The population prevalences for Alcohol and Cannabis Dependence were obtained from their respective publications[38,39].

Statistical Analyses

Models were fitted and compared utilizing confirmatory factor analysis (CFA), which is a form of Structural Equation Modeling (SEM). SEM is used to model the covariance among multivariate observations. In a CFA model, a set of correlated observed variables is represented by linear functions of a smaller number of latent (unobserved) factors. In particular, *p* multivariate observations (here, phenotypes or traits) are modeled by *m* latent factors as

$$\mathbf{y}_i = \mathbf{\Lambda}\boldsymbol{\eta}_i + \boldsymbol{\varepsilon}_i \tag{1}$$

where $\mathbf{y}_i$ is a $p \times 1$ vector of traits for person i; $\boldsymbol{\eta}_i$ is an $m \times 1$ vector of latent factors for person i; $\mathbf{\Lambda}$ is a $p \times m$ matrix of linear weights of each trait on the latent factors, known as factor loadings; and $\boldsymbol{\varepsilon}_i$ is a $p \times 1$ vector of residuals for the ith person on the p traits. The covariance structure of the CFA model is specified as

$$\mathrm{cov}[\mathbf{y}_i] = \mathbf{\Sigma}_y(\theta) = \mathbf{\Lambda\Psi\Lambda}' + \mathbf{\Theta} \tag{2}$$

where $\mathbf{\Sigma}_y(\theta)$ is a $p \times p$ model-implied covariance matrix of the traits for a set of model parameters θ, $\mathbf{\Psi}$ is an $m \times m$ matrix of the variances of and covariances among the latent factors, and $\mathbf{\Theta}$ is a $p \times p$ matrix of residual variances and covariances. Ultimately, the model-implied covariance structure is statistically compared with the covariance structure among the p observed traits to estimate model parameters and determine model fit.

In order to fit CFA models to psychopathology traits at the genomic level, we utilized the newly-proposed Genomic SEM software[18]. Genomic SEM employs a novel extension of the widely used LD-score regression[4,10] method to calculate the genetic covariance among traits using GWAS summary statistics from multiple studies. This

method accounts for potential sample overlap across studies through the LD-score intercepts. Genomic SEM results in a $p \times p$ genetic covariance matrix $\mathbf{S}$ containing SNP-based heritabilities on the diagonal and genetic covariances in the off-diagonal elements. Because $\mathbf{S}$ is estimated, the variability of its estimated elements is required for accurate model estimation. This is captured in a matrix $\mathbf{V}$, which contains squared standard errors of the estimates in $\mathbf{S}$ on the diagonal, and contains the covariance among parameter estimates in the off-diagonal. These off-diagonal terms capture potential sample overlap across traits.

Once the genetic covariance matrix is obtained, genomic CFAs are 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. The diagonally weighted least squares discrepancy function, denoted F_{WLS}, is expressed as

$$F_{WLS} = \left(\mathbf{S} - \boldsymbol{\Sigma}_y(\theta)\right)' diag(\mathbf{V})^{-1} \left(\mathbf{S} - \boldsymbol{\Sigma}_y(\theta)\right). \tag{3}$$

CFA estimation seeks parameter values in the system of equations in $\boldsymbol{\Sigma}_y(\theta)$ that minimize the discrepancy between the model-implied covariance matrix $\boldsymbol{\Sigma}_y(\theta)$ and the observed covariance matrix $\boldsymbol{S}_y(\theta)$.

Modeling Procedure

After GWAS summary statistics were identified for the 14 psychopathology traits of interest, the publicly-available results files were formatted for Genomic SEM preprocessing[18]. Next, the genetic covariance matrix was calculated using LD weights

for populations of European descent provided by the Broad Institute and the ldsc function of the Genomic SEM R package. The genetic covariance matrix $\mathbf{S}$ and its associated sampling matrix $\mathbf{V}$ were then used for model fitting. In addition to obtaining estimates of model parameters from the discrepancy function in Equation (3), measures of overall model fit were obtained. To evaluate model fit, we used the Comparative Fit Index (CFI), the Bayesian Information Criterion (BIC) and the Root Mean Square Residual (RMSR), which provide absolute and relative (BIC) indices of model fit.

User-defined models were provided to the Genomic SEM software in the lavaan syntax[22]. CFA models were specified *a priori* with increasing complexity to evaluate and contrast different hypotheses regarding the latent factor structure of psychopathology. First, a general factor model was fitted with only one latent variable on which all traits had a factor loading. A model with three correlated domains of psychopathology (Externalizing, Internalizing, and Thought Problems) was then fitted. These factors were allowed to correlate because they are not expected to operate on the observed traits in isolation. Next, a bifactor model structure was specified, in which the three specific factors were uncorrelated and an additional uncorrelated general factor was included. In the confirmatory bifactor model, all traits have loadings on two uncorrelated factors – a loading on the general factor, and a loading on one and only one of the three domain-specific factors (Externalizing, Internalizing, and Thought Problems). This structure implies that all of the traits *across* domains are correlated with each other due only to their factor loadings on the general factor, whereas the

correlation among traits *within* psychopathology domains are also correlated with each other due their factor loadings on the domain-specific factors.

After the bifactor structure, a 4th hypothesized correlated factor defining the substance use traits (Alcohol Dependence, Cannibis Dependence, and Tobacco Use) was added to the model containing the three correlated factors. A 5th model tested for an additional Neurodevelopmental Disorders (NDD) factor comprising the childhood disorders and traits (ADHD, ASD, and Aggression) to capture remaining correlations among these traits, over and above the 3 correlated factors. This model resulted in unstable parameter estimates when the NDD factor was correlated with the other factors, so it was specified as orthogonal to the other factors.

Other models were examined based on alternative hypothesized structures of psychopathology in the literature; the fit of these models appear in the bottom of Table 1. In addition, to achieve sensible model fit and parameter estimates, the bifactor model was re-estimated constraining all of the traits' residual variances to be greater than zero. With these constraints, good model fit was achieved, but parameter estimates and their standard errors for the specific factors were unstable (see Supplementary Table 3).

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Table 1. Models and Model Fit Statistics

Model	χ^2	df	BIC	CFI	SRMR
1. One common factor	932	77	1319	.62	0.181
2. Distinct but correlated factors for EXT, INT, and TP	694	74	1123	.73	0.149
3. A bi-factor model, with an overarching general psychopathology factor and three uncorrelated specific factors (EXT, INT, and TP)	132506	63	133086	-57.57	0.131
4. Is there a 4th distinct factor representing substance use?	741	71	1196	.70	0.152
5. Is there evidence for a neurodevelopmental factor (ADHD, ASD, and aggression), distinct from adult psychopathology?	505	71	924	.81	.140
6. Do ADHD, ASD, and aggression load only on NDD factor?	468	71	923	.82	.142
7. Does Bipolar load onto both TP and EXT?	658	73	1087	.74	.148
8. Does Bipolar load onto both TP and INT?	49443	73	49872	-20.83	.146
9. Does OCD load on INT as well as TP?	695	73	1124	.72	.149
10. Do Eating Disorders load on INT as well as EXT?	536	73	965	.80	.140
11. Bifactor model with constraints	453	63	1016	.83	.130

NOTE: EXT, Externalizing factor; INT, Internalizing factor; TP, Thought Problems factor; df, degrees of freedom; BIC, Bayesian Information Criterion; CFI, Comparative Fit Index; SRMR, Standardized Root Mean Residual.

Figure 1 Heatmap of Genetic Correlations among Disorders and Traits

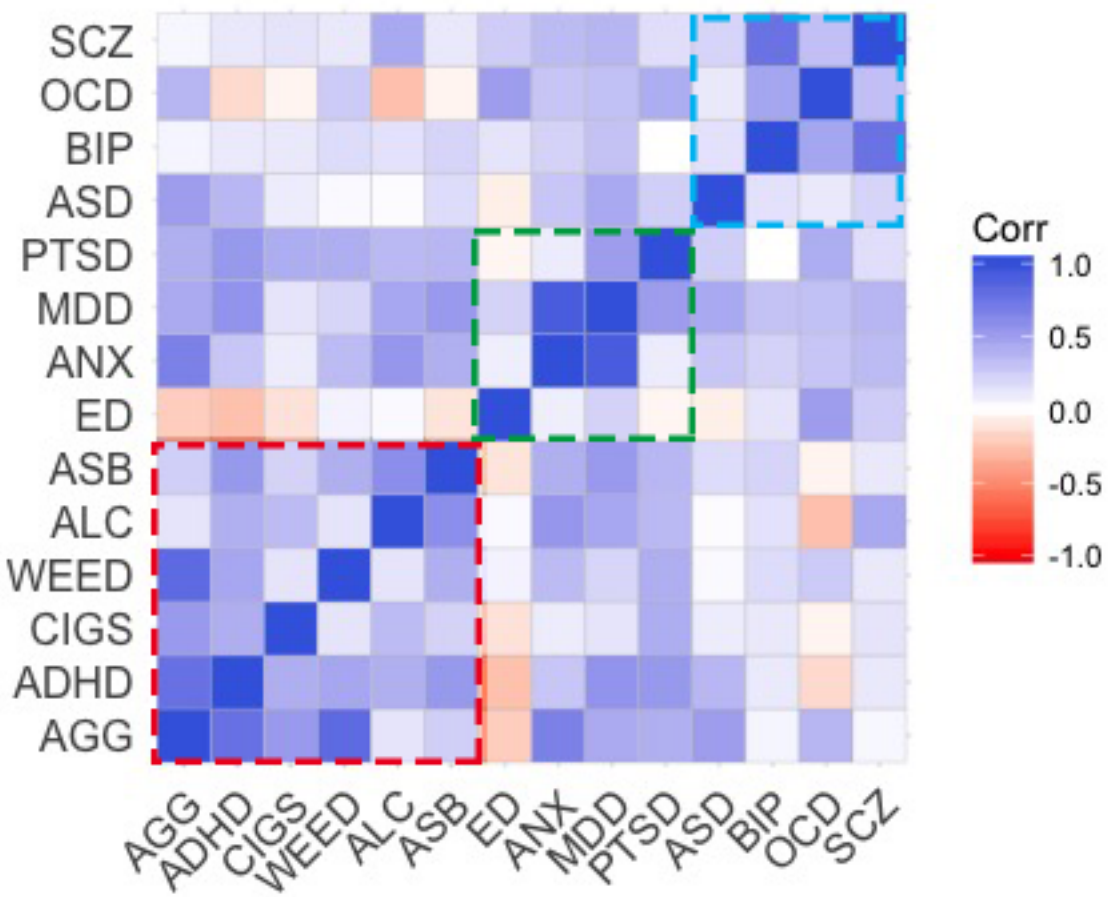


Figure 2. Best-Fitting CFA Model

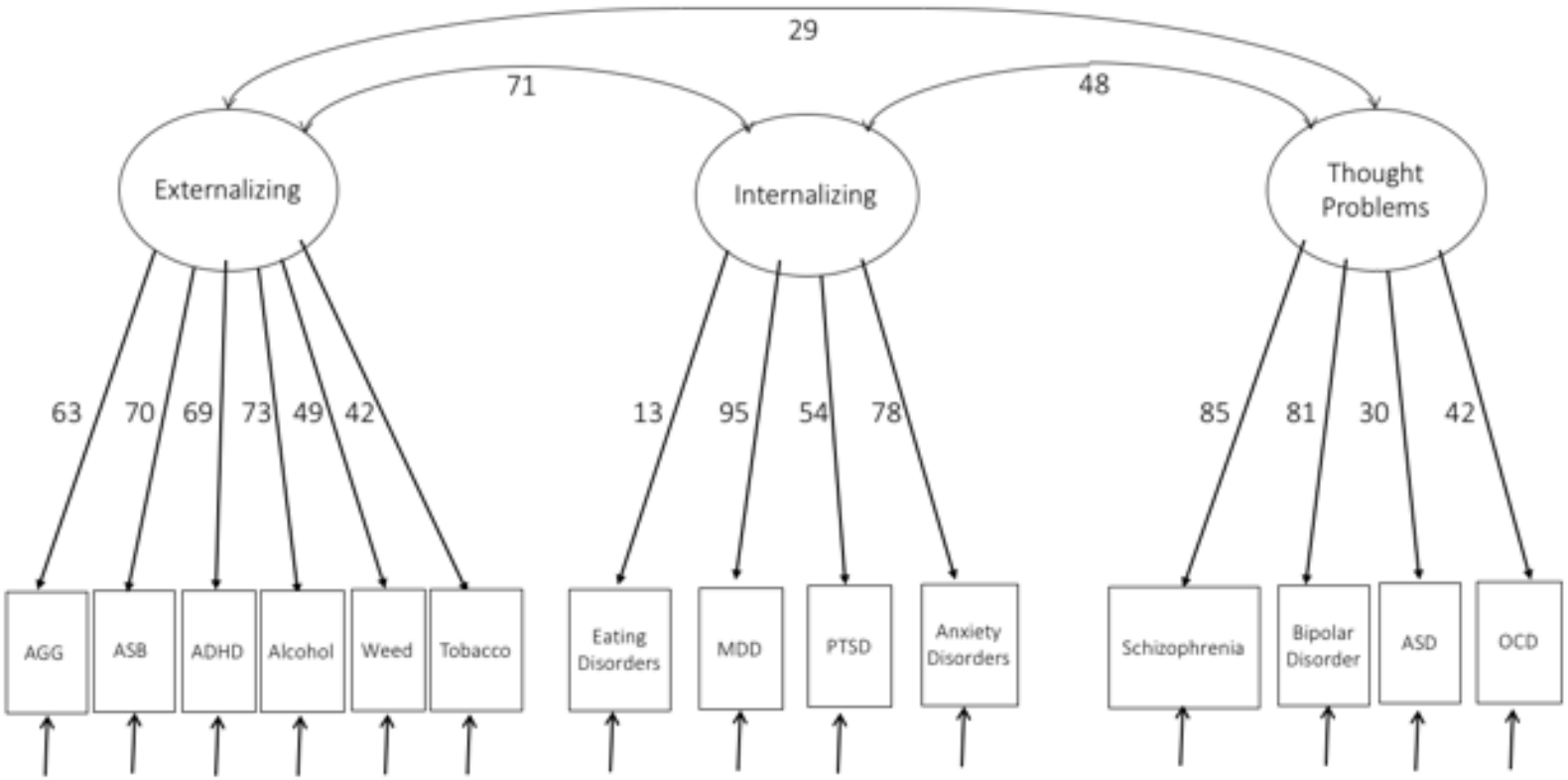


Figure 3. Best-Fitting CFA Model – Including the Neurodevelopmental Disorders Factor

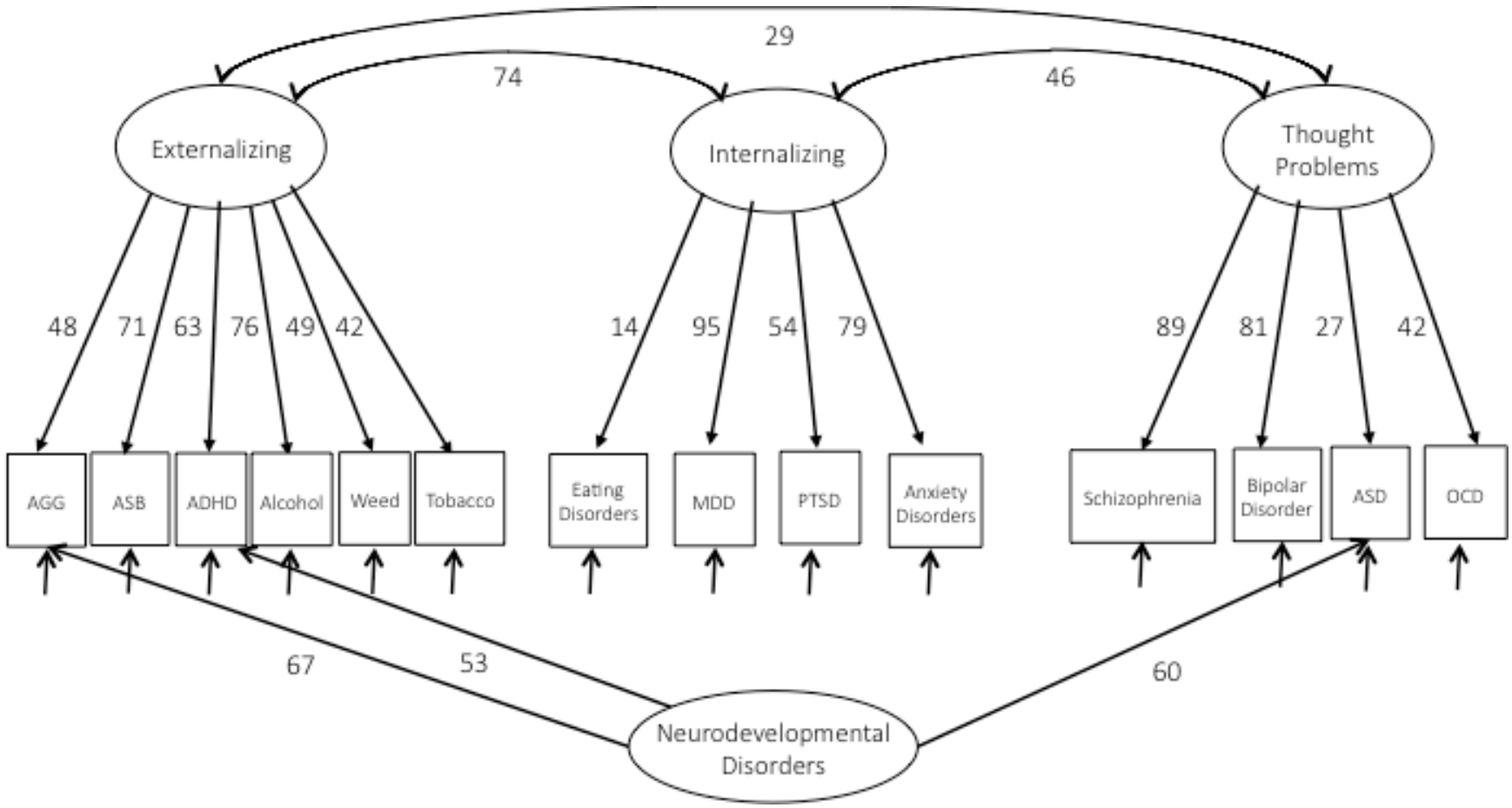
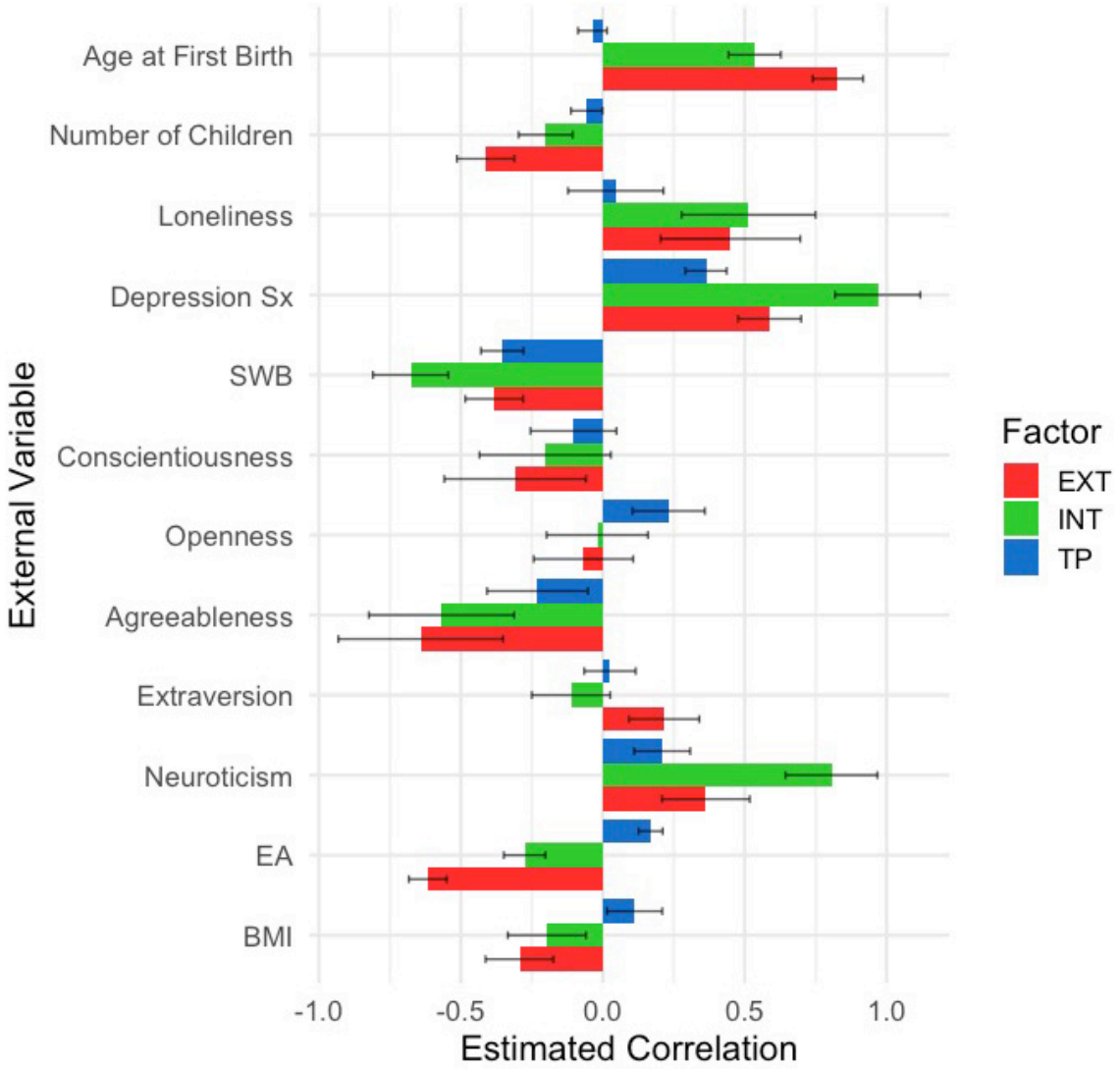


Figure 4. Genetic Correlations of the External Validity Variables with the Three Higher-Order Factors



Supplemental Materials

Supplementary Table 1. Characteristics of Studies Included in Analyses

Phenotype	Study	Year	Data Source	Sample Size (cases/ controls)	Sample/Pop Prevalence	Study Design	Effect	Published h2 (SE)	gSEM h2 (SE
ADHD	DeMontis et al.[1]	2017	PGC-iPSYCH	20,183/ 35,191	.36/ .111	Case-control	OR	.22 (.01)	.16
Alcohol Dependence	Walters et al.[2]	2018	PGC	10,206/ 28,480	.26/ .1235	Case-control	OR	.09 (.02)	.12
Cannabis Dependence	Agrawal et al.[3]	2018	PGC	3,757/ 9,931	.26/ .0236	Case-control	Beta		.03
Tobacco Use	TGC[4]	2010	TGC	73,853	NA/ NA	Continuous	Beta		.03
Aggression	Pappa et al.[5]	2016	EAGLE	18,988	NA/ NA	Continuous	Beta	.10 (.06)	.05
Antisocial Behavior	Tielbeek et al.[6]	2017	BroadABC	16,400	NA/ NA	Continuous	Beta	.05 (.03)	.05
Anorexia	Duncan et al.[7]	2017	PGC	3,495/ 10,982	.17/.021	Case-control	OR	.20 (.02)	.22
Anxiety Disorders	Otowa et al.[8]	2016	ANGST/PGC	7,016/ 14,745	.32/ .191	Case-control	Beta	.10 (.04)	.13
PTSD	Duncan et al.[9]	2017	PGC	2,424/ 7,113	.25/ .071	Case-control	OR	.12 (.05)	.13
MDD	Wray et al.[10]	2018	PGC-iPSYCH	59,851/ 113,154	.35/ .071	Case-control	OR	.09 (.004)	.08
OCD	IOCDF-GC & OCGAS[11]	2017	PGC	2,688/ 7,037	.28/ .021	Case-control	OR	.28 (.04)	.26
Schizophrenia	Schizophrenia Working Group of the PGC[12]	2014	PGC	36,989/ 113,075	.25/ .011	Case-control	OR	.45 (.02)*	.19
Bipolar Disorder	Sklar et al.[13]	2011	PGC	7,481/ 9,250	.45/ .011	Case-control	OR	.43 (.04)*	.26
ASD	Grove et al.[14]	2017	PGC-iPSYCH	18,382/ 27,969	.40/ .021	Case-control	OR	.12 (.01)	.12

Note. IOCDF = International Obsessive Compulsive Disorder Foundation Genetics Collaborative, OCGAS = OCD Collaborative Genetics Association Studies, TGC = Tobacco and Genetics Consortium. *SNP-based heritability obtained from LD Hub when h^2_{SNP} was not reported in the published paper. [1]NIMH, 2018 [35]Walters et al., 2018 [36]Agrawal et al. 2018.

Supplemental Table 2. Factor Loadings and SEs – with NDD factor

Disorder/Trait	Standardized loading	SE
Externalizing		
ADHD	.63	.06
ASB	.71	.12
Aggression	.48	.13
Tobacco	.42	.08
Alcohol	.76	.08
Cannabis	.49	.17
Internalizing		
PTSD	.54	.09
Anxiety	.79	.09
MDD	.95	.09
Anorexia	.14	.06
Thought Problems		
Schizophrenia	.89	.06
ASD	.27	.04
Bipolar	.81	.06
OCD	.42	.05
Neurodevelopment		
ASD	.60	.19
Aggression	.67	.20
ADHD	.53	.18

Supplemental Table 3. Specific Factor Loadings and SEs – Bifactor model with constraints

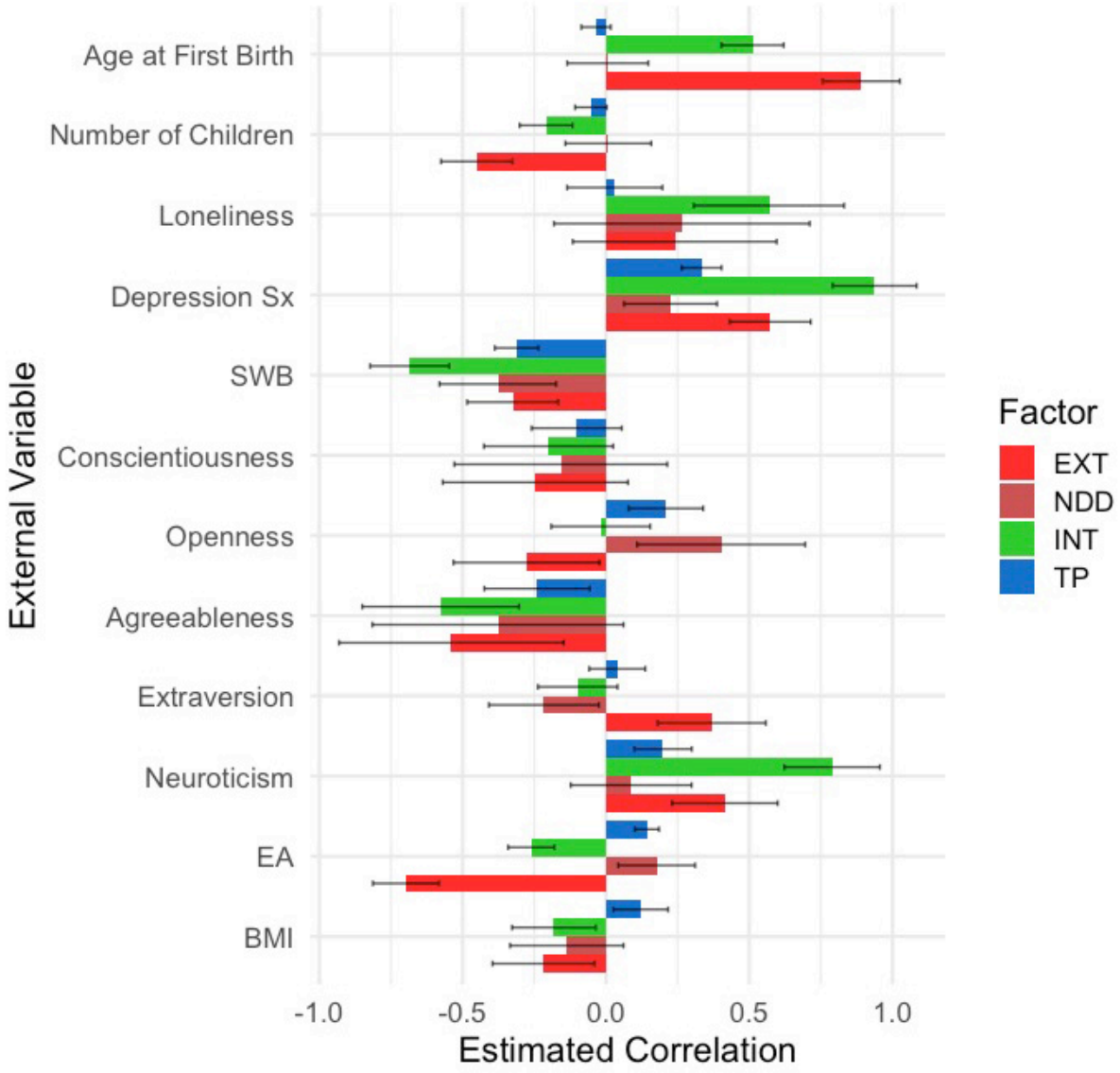
Disorder/Trait	Standardized loading	SE
Externalizing		
ADHD	.75	.23
ASB	.37	.18
Aggression	.59	.23
Tobacco	.43	.15
Alcohol	.17	.12
Cannabis	.43	.27
Internalizing		
PTSD	-.55	.51
Anxiety	.33	.30
MDD	.33	.26
Anorexia	.31	.25
Thought Problems		
Schizophrenia	.67	.10
ASD	.04	.05
Bipolar	.97	.15
OCD	.38	.07

Supplemental Table 4. Characteristics of External Validity Variables

Phenotype	Study	Year	Data Source	Sample Size	Study Design	Effect	Published h^2 (SE)	gSEM h^2 (SE)	Ancestry
Neuroticism	Okbay et al.[15]	2016	SSGAC	298,420	Continuous	Beta	.09 (.01)	.03	European
Depression Symptoms	Okbay et al.[15]	2016	SSGAC	161,460	Continuous	Beta	.05 (.004)	.10	European
Subjective Wellbeing	Okbay et al.[15]	2016	SSGAC	298,420	Continuous	Beta	.04 (.002)	.10	European
Extraversion	Van Den Berg et al.[16]	2015	GPC	170,910	Continuous	Beta	.05 (.07)	.04	European
Agreeableness	De Moor et al.[17]	2012	GPC	20,669	Continuous	Beta	--	.01	European
Conscientiousness	De Moor et al.[17]	2012	GPC	20,669	Continuous	Beta	--	.06	European
Openness	De Moor et al.[17]	2012	GPC	20,669	Continuous	Beta	--	.10	European
Educational Attainment	Lee et al.[18]	2018	SSGACE	766,345	Continuous	Beta	.15 (.01)	.11	European
Loneliness	Gao et al.[19]	2016	PGC	10,760	Continuous	Beta	.16 (.06)	.11	Admixed
Body Mass Index	Yengo et al.[20]	2018	GIANT + UK Biobank	681,275	Continuous	Beta	.25 (.01)*	.15	European
Number of Children	www.nealelab.is/uk-biobank	2018	UK Biobank	180,952	Continuous	Beta	.06 (.01)	.06	European
Age at First Birth	www.nealelab.is/uk-biobank	2018	UK Biobank	123,846	Continuous	Beta	.17 (.01)	.17	European

*SNP-based heritability from the UK Biobank, as h^2_{SNP} for the combined samples was not reported in the original paper.

Supplemental Figure 1. Genetic Correlations of the External Validity Variables with the Four Higher-Order Factors



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