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Exploration of Dimensional Structure of Major Psychiatric Disorders Reveals Relationship with Substance Use and Personality

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Table of Contents

Abstract

Objective: Using a mixture of statistical techniques like structural equation modeling, confirmatory, and exploratory factor analyses, we aimed to determine the genetic factor structure among Externalizing, Internalizing, and Psychotic spectrum disorders through methods that evaluate GWAS-based correlations. Additionally, a subsequent factor analysis based on the most suitable psychiatric model was conducted to understand how non-clinical behavioral traits align with this factor structure.

Methods: Publicly available GWAS summary statistics for twelve major psychiatric disorders, six substance use measures and two personality domains were incorporated into structural equation models. Using the GenomicSEM software package, GWAS-based correlations were estimated between all twelve disorders and eight non-clinical traits before applying exploratory (EFA) and confirmatory factor analyses (CFA) to identify the genetic factor structure.

Results: EFA of the twelve psychiatric disorders indicated that a three-factor model (Internalizing, Externalizing, Psychotic) best fit the data. Internalizing, Externalizing, and Psychotic dimensions were moderately correlated. A secondary CFA of non-clinical traits indicated that substance use and risk-taking were genetically related to the Externalizing factor, high levels of neuroticism were associated with the Internalizing factor.

Conclusions: The present results corroborate prior research from twin, family, and other molecular studies on the factor structure of DSM-based psychiatric disorders. Significant associations were detected between the latent factors and non-clinical psychosocial measures of behavior. These additional measures highlight the importance of including sub-clinical, behavioral phenotypes in studying the comorbidity of psychiatric illness.

Exploration of Dimensional Structure of Major Psychiatric Disorders Reveals Relationship with Substance Use and Personality

Literature Review

Current Study

One of the most notable and replicable findings in psychiatric research is the high rate of comorbidity among psychiatric disorders with up to two-thirds of individuals who meet criteria for one disorder meeting criteria for a second (Caspi et al., 2018). The field of psychopathology has been significantly shaped by the emergence and evolution of factor analytic models, driving a paradigm shift from categorical to dimensional approaches in understanding the comorbidity among mental disorders. A pivotal part of this shift is the development of factor models that group genetically similar disorders along a continuum. However, the results from this body of literature are quite heterogenous. This heterogeneity is likely due to study design choices made by researchers such as analyzing only certain subsets of disorders or using data that is based on clinical diagnosis rather than reported symptomatology. The following literature review highlights significant remaining gaps: a comprehensive model of both common and rare psychiatric disorders as well as non-clinical measures of substance use and personality has not emerged from factor analytic methods. The objective of the current study is to determine the joint factor structure of 12 psychiatric disorders and 8 non-clinical measures of substance use and personality using a recent method of genomic structural equation modelling that relies on GWAS-based genetic correlations. Although there is some support for a correlated three-factor model of psychopathology, the authors decided to take an exploratory approach due to the

paucity of studies including less common psychiatric disorders such as ADHD, ASD, eating disorders (ED), OCD, PTSD, and Tourette's.

Etiology of the Internalizing-Externalizing Factors

The origin of factor analytic models of psychopathology began with child psychiatrists trying to develop more comprehensive systems of diagnostic classification for children by examining the interrelationships among clusters of psychiatric symptoms during the 1950s-1960s (Achenbach et al., 1978). Only two diagnostic categories for children were included in the first edition of the Diagnostic and Statistical Manual (DSM-I; 1952): Adjustment Reaction and Childhood Schizophrenia. Motivated by this lack of diagnostic discrimination, Thomas Achenbach (1966) constructed the first factor analytic model of psychopathology in which he collected data on psychiatric symptoms from 300 male and 300 female child patients. His analysis found that symptoms clustered at two levels: a broad level split between Internalizing and Externalizing symptoms, and a narrower level including specific syndromes. Some of these syndromes resembled established psychiatric diagnoses, while others seemed specific to certain stages of development. The overall results showed that the factors obtained can be used directly for the classification of child psychiatric cases for research purposes.

In subsequent factor analyses relying on diagnostic outcomes rather than symptoms, the internalizing factor has been found to reliably consist of mood and anxiety disorders such as major depressive disorder (MDD), generalized anxiety disorder (GAD), phobias, and obsessive-compulsive disorder (OCD) (Krueger, 1999) (Kendler et al., 2003). While the externalizing factor generally consists of attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), antisocial personality disorder (ASPD), and substance use disorders.

Etiology of the Schizophrenia Spectrum

Expanding the scope of understanding beyond the internalizing and externalizing factors, researchers have also delved into the etiology of the factor structure of psychotic-based disorders. Tsuang et al. (1983) began with testing the main hypothesis underlying the notion of the schizophrenia spectrum: that a range of disorders of varying severity share the same underlying familial vulnerability with schizophrenia (Kendler et al., 1995). The authors formally tested this hypothesis by comparing morbidity risks for psychiatric illnesses in the first-degree relatives of schizophrenics and controls (Tsuang et al., 1983). Both descriptive analysis and a multiple threshold model were applied to the family data to detect a cluster of conditions which may share an underlying familial etiology with schizophrenia. The proportion of relatives receiving any psychiatric diagnosis other than schizophrenia and affective disorder was not statistically different from controls. Subsequent testing of the multiple threshold model indicated that it was a poor fit to the data. Consequently, no support was found for the schizophrenia spectrum.

Another family study testing the schizophrenia spectrum hypothesis found conflicting evidence in support of familial aggregation. Baron et al. (1987) analyzed data from chronic schizophrenic, schizotypal, and normal control probands using multivariate-multifactorial genetic models. Results were consistent with multifactorial inheritance in which chronic schizophrenia and schizotypal personality disorder represent different phenotypic manifestations of a single continuum of genetic and environmental liability.

Given the disparate results from these two studies and their limitations (small sample size, limited assessment of schizophrenia spectrum personality disorders in relatives, and a narrow range of proband diagnoses), Kendler et al. (1995) sought to assess the validity of the

spectrum hypothesis with data from the Roscommon Family Study using a more comprehensive range of schizophrenia subtypes and significantly larger sample. The schizophrenia spectrum hypothesis predicts that the correlations in liability to schizophrenia spectrum disorders between probands and first-degree relatives should be equal for all the diagnostic classes under the multiple threshold model. This model fit the data significantly better than the first model which allowed the correlations in liability to differ. Despite finding substantial evidence in favor of the hypothesized schizophrenia spectrum, the authors were unable to establish a definitive severity order for the diagnostic categories within this spectrum. They suggest that schizophrenia is likely at the most severe end of the spectrum, and psychotic affective illness is likely at the milder end. Results here were replicated and extended to include affective illness within the Roscommon Family Study (Kendler et al., 1998). The risks for schizophrenia and schizophrenia spectrum disorders were significantly increased in relatives of all proband classes except major depression. This increase was moderate for bipolar-schizomanic probands, substantial for schizophrenic, schizophreniform, and schizodepressed probands, and marked for hebephrenic probands.

While initial studies presented conflicting evidence, subsequent research, particularly the comprehensive Roscommon Family Study, provided more robust support for the spectrum hypothesis. The nuanced findings from these studies underscore the complexity of psychotic-based disorders and their familial underpinnings. With the schizophrenia spectrum reasonably established, the next phase for researchers was to examine how other disorders, beyond the boundaries of this spectrum, fit into the broader factor structure.

Replication and Extension of Factors in Twin Studies

Twin studies provide distinct advantages over family studies by controlling for age and cohort effects, allowing for the estimation of genetic as well as environmental factors and

heritabilities, and examining non-additive genetic effects. The classical twin study compares the similarity of monozygotic (identical) and dizygotic (fraternal) twins reared together to estimate the relative contributions of genetics and environment to a particular trait or condition (Galton, 1875). This study design has been extended to the multivariate case to "test hypotheses about the genetical and environmental *sources* of variation simultaneously with psychological hypotheses about the contribution of these sources to the *structure* of covariation between variables and the residual variation specific to particular variables" (Martin et al., 1979).

Since the establishment of the schizophrenia spectrum, researchers had wanted to answer the question of whether other psychoses, not just subtypes of schizophrenia, fit into the same continuum of genetic liability. Twin pairs (106 monozygotic and 118 same-sex dizygotic pairs) were ascertained from the Maudsley Twin Register in London to determine whether operationally defined schizophrenia, schizoaffective, and manic (bipolar disorder) syndromes share genetic risk factors (Cardno et al., 2002). The model fitting showed significant genetic correlations between all three syndromes. There was evidence of both common and syndrome-specific genetic contributions to the variance in liability to the schizophrenic and manic syndromes, but the genetic liability to the schizoaffective syndrome was entirely shared in common with the other two syndromes. In contrast, environmental liability to the schizoaffective syndrome was not shared with the other syndromes. This study provides partial support for the inclusion of mania (bipolar disorder) within the psychotic spectrum.

A review of twin, family, and other genetic and phenotypic studies on bipolar disorder, unipolar depression, and schizophrenia in relation to 11 validating criteria proposed by the DSM-V Task Force Study Group came to a similar determination about the inclusion of bipolar disorder in the clustering of psychotic disorders (Goldberg et al., 2009). In conclusion, the

authors state, " Delusions and hallucinations are shared between them [schizophrenia and bipolar disorder], and although high negative affect characterizes the emotional cluster, it is not a marked feature of either of the psychoses. In this formulation, schizophrenia and BPD are looked upon as being at different ends of a psychosis continuum, with neural abnormalities, birth trauma and negative symptoms at one end, and affective symptoms and a somewhat better outcome at the other; differences between them are seen as quantitative, rather than each being a discrete disease entity".

Most studies investigating the factor structure of psychopathology have primarily ascertained data on common psychiatric disorders and as a consequence there is relatively sparse evidence for where rare or less common illnesses such as neurodevelopmental disorders fit (Wright et al., 2013). There are, however, a few twin studies that have examined these disorders. One such study analyzed questionnaire data on symptoms related to a neurodevelopmental disorder (ADHD) and an externalizing disorder (conduct disorder) using bivariate genetic analysis and a liability threshold model approach (Thapar et al., 2001). Common genetic factors and non-shared environmental influences were the driving forces behind the co-occurrence of ADHD and conduct problems. However, these two categories seemed to have unique characteristics as extra environmental factors played a role in conduct problems. The combination of ADHD and conduct disorder (ADHD+CD) seemed to be a more genetically severe version of ADHD. Another twin study used bivariate twin models to assess the extent to which individual differences in autistic (ASD) traits and ADHD traits were caused by genetic and environmental influences, and the extent to which they were caused by the same or different genetic and environmental influences (Ronald et al., 2008). The research suggests that both ASD and ADHD whether considered as quantitative traits or extreme forms, exhibit strong genetic

inheritance. There appears to be a fair amount of genetic influences shared by these behaviors, as well as distinct genetic influences specific to each. These findings were consistent across data gathered from parents and teachers, despite relying on different measurement methods. Furthermore, they aligned with the only other similar twin study which examined this association (Constantino et al., 2003). Both report evidence that variation in behaviors characteristic of ADHD explain a significant proportion of variation in autistic traits.

The classical twin study design, with its ability to disentangle genetic and environmental contributions, has been instrumental in shedding light on the genetic liability shared across different psychotic disorders. The inclusion of bipolar disorder within the psychotic spectrum, as evidenced by studies like those of Cardno et al. and Goldberg et al., underscores the continuum of genetic liability that spans across different disorders. Furthermore, the exploration into less common illnesses, such as neurodevelopmental disorders, adds another layer of complexity to our understanding. The genetic overlap between disorders like ADHD and conduct disorder, as well as between ASD and ADHD traits, suggests that many psychiatric conditions may not be entirely distinct entities but rather points on a broader spectrum of genetic liability.

Integrating the Three Factors of Psychopathology

The absence of schizophrenia and schizophrenia subtypes in the factor structure of psychopathology motivated Kotov et al. (2011) to determine how schizophrenia and schizotypal personality disorder (referred to by the authors as the schizophrenic factor) fit into a factor model with other well-established Internalizing and Externalizing disorders (Internalizing = MDD, OCD, social anxiety, panic attack; Externalizing = antisocial personality disorder, conduct problems, alcohol use disorder, cannabis use disorder, and other drug use disorder) based on data from a county-wide cohort with first-admission psychosis. A key advantage of ascertaining

individuals from a severely ill population compared to studying twins is that it makes possible the examination of less common disorders that are rare in the general population. Kotov et al. used confirmatory factor analysis (CFA) to compare the fit of four different models: (1) Factors based on the DSM-IV, grouping variables into five clusters (anxiety, mood, schizophrenia, substance use, personality disorder) (2) three factors: internalizing, externalizing, and schizophrenic (schizophrenia/schizotypal personality) (3) two factors (EXT and INT) with the schizophrenia phenotypes loading onto the externalizing factor and (4) two factors (EXT and INT) in which schizophrenia phenotypes loaded onto the internalizing factor. CFA indicated that the five factor DSM model poorly fitted the data, while both two factor models represented the data equally well. Factor analysis implicates the three-factor model as the best-fitting model.

The correlated three-factor structure has also been replicated in a community-based sample with data collected from the 2007 Australian National Survey of Mental Health and Wellbeing, a nationally representative epidemiological survey of mental and substance use disorders (Wright et al., 2013). The paper presents a comparison of ordered latent class and latent trait models to understand the nature of psychopathological variation in 33-symptom level indicators. Six distinct dimensions of variation were identified: distress, obsessive-compulsivity, fear, alcohol problems, drug problems, and psychotic experiences. Next, they fit these domains into confirmatory factor models to understand the hierarchical structure. In this process, latent trait scores were calculated for each domain and used as observed variables in the model. To establish a baseline for comparison, a one-factor model was created, even though it was predicted to not provide the best fit based on previous research. Following this, two two-factor Internalizing-Externalizing models were constructed. In the first model, the internalizing factor consisted of distress, obsessive-compulsivity, and fear; externalizing included alcohol and drug

problems, with psychotic experiences loaded onto internalizing. The second model was similar, but psychotic experiences were loaded onto the externalizing factor instead. In the end, a three-factor hierarchical model that separated psychotic experiences from the Internalizing and Externalizing domains was shown to provide the best fit. The correlations among these higher-order factors were .48 (Externalizing with Internalizing), .59 (Psychosis with Internalizing), and .36 (Psychosis with Externalizing). This study therefore suggests that psychopathology in the community can be best represented by a model that conceptualizes internalizing, externalizing, and psychosis as three distinct, but correlated, higher-order latent traits.

The Role of Personality

As another approach to explain the comorbidity among psychiatric phenotypes, researchers have examined whether or not the observed structure of psychopathology holds or remains invariant when including non-clinical measures of personality and behavior. Hink et al.'s (2013) multivariate genetic analyses of 1,326 twin pairs aged 12 to 18 years determined whether there are common genetic and environmental influences among three internalizing disorders (MDD, GAD, SAD), three externalizing disorders (ADHD, ODD, CD), and two personality traits (neuroticism and novelty seeking). Their findings indicate that internalizing disorders (e.g., depression, anxiety) are more closely correlated with each other (.38 average), as are externalizing disorders (.39 average), rather than between internalizing and externalizing disorders (.31 average). Neuroticism was moderately correlated with both types of disorders, while novelty seeking was moderately correlated with the externalizing disorders and only minimally with MDD among the internalizing disorders. The cross-trait, cross-twin correlations among MZ twins were larger than among DZ twins for both personality variables and the psychopathology variables, indicating a genetic influence on these traits and disorders.

There were also significant genetic influences from the latent internalizing and externalizing factors on MDD, GAD, SAD, ADHD, ODD, and CD, suggesting a significant genetic component to these disorders. In the independent pathway model, the magnitude of the effect of the latent genetic internalizing factor on GAD and that of the latent genetic externalizing factor on ADHD was near zero when the genetic influences shared with novelty seeking and neuroticism were controlled for. The paper concludes that genetic influences shared in common with neuroticism and novelty seeking significantly influence the psychiatric disorders investigated, with the exception that nonshared environmental influences associated with neuroticism did not significantly influence CD. Moreover, genetic influences shared with novelty seeking explained 4-16% of the variance in disorders, while those shared with neuroticism explained 11-22% of the variance. Furthermore, nonshared environmental influences shared with neuroticism explained 1-4% of the variance in disorders, with the exception of CD. In the reduced model, shared environmental influences could be dropped entirely, suggesting that the shared environment does not play a significant role in these disorders after accounting for genetic influences. The results suggest that genetic influences play a significant role in the covariation among and between internalizing and externalizing disorders, whereas nonshared environmental influences explained less of the covariation, with none of the covariation between CD and other disorders being explained by nonshared environmental influences.

More comprehensive measures of personality have been studied alongside psychopathology in which normative as well as pathological personality were assessed in a factor analysis along with 11 psychiatric disorders from a population-based sample of Norwegian twins (Rosenström et al., 2019). The minimum number of factors to adequately describe the data was determined to be three (a general factor of psychopathology, a factor specific to internalizing

disorders/traits, and a factor specific to externalizing disorders/traits). Neuroticism (r = -.39) and extraversion (r = .46) were found to be significantly correlated with the factor specific to externalizing disorders/traits in the bi-factor model (general factor loads onto all disorders and almost all personality traits, while the internalizing and externalizing factors which are orthogonal with the general factor have loadings on the typical internalizing and externalizing disorders and some of the associated personality traits). Evidence here indicates a relationship between personality (neuroticism and extraversion) and domain-specific psychopathology (a risk factor for externalizing disorders/traits). The factor structure of psychiatric disorders remains unchanged when including measures of personality. These findings suggest that to holistically understand the landscape of psychiatric disorders, it is imperative to consider both clinical and non-clinical measures.

Aims and Hypotheses

Aims

The aim of this study is to explore the factor structure of psychopathology—specifically, Externalizing, Internalizing, and Psychotic spectrum disorders—using molecular data and summary statistics from the latest GWAS. Furthermore, we will incorporate non-clinical measures, such as lifetime cannabis use and neuroticism, to assess the consistency of this factor structure across different assessment methods.

Aim 1. Test competing hypotheses regarding the sources of comorbidity between psychiatric disorders.

We aim to explore the covariance between twelve psychiatric disorders using factor analysis. We will test how disorders such as MDD, PTSD, ANX, SCZ, BP, ADHD, AUD, and CUD relate to potential underlying dimensions of psychopathology. Given the limited analyses involving ASD, ED, OCD, and TS, this research will also examine their relationship with these dimensions without making a priori assumptions. We hypothesize that a correlated three-factor model will best explain the interrelationships among psychiatric disorders.

Aim 2. Test competing hypotheses regarding the sources of comorbidity between psychiatric disorders and non-clinical measures of personality and substance use.

We aim to explore how the addition of the 8 non-clinical measures of personality/behavior influences the factor structure identified in aim 1. Specifically, we will investigate whether these measures align with or diverge from the previously identified factors, without making a priori assumptions about the resulting structure. We hypothesize that the factor structure of psychopathology will remain invariant when including non-clinical measures of personality/behavior.

Data Overview

Summary Data

We collected the most recent, publicly available GWAS summary statistics for the phenotypes of interest (see Table 1). These data came from a few large cohorts and many smaller ones. The largest consortia include the Psychiatric Genomics Consortium (PGC), GWAS & Sequencing Consortium of Alcohol and Nicotine use, Social Science Genetic Association Consortium (SSGAC), Million Veteran Program (MVP), iPSYCH, deCODE, and UK Biobank. The primary traits were 12 major psychiatric disorders from the DSM-IV and DSM-V. Non-

clinical phenotypes include 8 measures of substance use and personality for a total of twenty traits. Sample summaries are available in the Table 1 and more detailed descriptions are listed in the following section.

Table 1. Sample Characteristics

Traits	N	Cases	Controls	Sample Prevalance	Population Prevalance
1. Major Depressive Disorder (MDD) (Howard et al., 2019)	807,553	246,363	561,190	0.30	0.30
2. Bipolar Disorder (BP) (Mullins et al., 2021)	413,466	41,917	371,549	0.11	0.01
3. Schizophrenia (SZ) (Trubetskoy et al., 2022)	130,644	53,386	77,258	0.41	0.01
4. Attention-Deficit/Hyperactivity Disorder (ADHD) (Demontis et al., 2019)	55,374	20,183	35,191	0.36	0.05
5. Posttraumatic Stress Disorder (PTSD) (Nievergelt et al., 2019)	174,659	23,212	151,447	0.13	0.08
6. Autism Spectrum Disorder (ASD) (Grove et al., 2019)	46,351	18,382	27,969	0.40	0.01
7. Tourette's syndrome (TS) (Yu et al., 2019)	14,307	4,819	9,488	0.34	0.01

Traits	N	Cases	Controls	Sample Prevalance	Population Prevalance
8. Anxiety Disorders (ANX) (Levey et al., 2020)	192,256	28,525	163,731	0.15	0.20
9. Eating Disorders (ED) (Watson et al., 2019)	72,517	16,992	55,525	0.23	0.01
10. Obsessive-Compulsive Disorders (OCD) (IOCDF-GC and OCGAS, 2018)	9,725	2,688	7,037	0.28	0.03
11. Alcohol Dependence (AD) (Walters et al., 2018)	46,568	11,569	34,999	0.25	0.18
12. Cannabis use disorder (CUD) (Johnson et al., 2020)	374,287	17,068	357,219	0.05	0.09
13. Problematic alcohol use (PAU) (Zhou et al., 2020)	435,563	NA	NA	NA	NA
14. Lifetime cannabis use (LCU) (Pasman et al., 2018)	162,082	52,758	109,324	0.33	0.33
15. Drinks per week (DPW) (Liu et al., 2019)	941,279	NA	NA	NA	NA
16. Cigarettes per day (CPD) (Liu et al., 2019)	337,334	NA	NA	NA	NA
17. Smoking initiation (SI) (Liu et al., 2019)	1,232,091	933,309	298,782	0.76	0.52

Traits	N	Cases	Controls	Sample Prevalance	Population Prevalance
18. Neuroticism (NEU) (Baselmans et al., 2019)	523,783	NA	NA	NA	NA
19. Extraversion (EXTRA) (Van Den Berg et al., 2016)	63,030	NA	NA	NA	NA
20. Risk-taking (RISK) (Linner et al., 2019)	466,571	NA	NA	NA	NA

NA values indicate continuous traits and entries 1-12 are clinical traits and 13-20 are non-clinical.

Phenotypic Measures

GWAS Summary Statistics for Clinical Phenotypes

Major depressive disorder (MDD) — MDD GWAS summary statistics were based on a GWAS meta-analysis of three studies (UK Biobank, 23andMe, and Psychiatric Genomics Consortium), totaling 246,363 cases and 561,190 controls (Howard et al., 2019). UK Biobank used a broad definition of depression where case and control status was defined by participants' response to the questions, "Have you ever seen a general practitioner for nerves, anxiety, tension, or depression?" or "Have you ever seen a psychiatrist for nerves, anxiety, tension, or depression?". Participants were excluded if they identified with bipolar disorder, schizophrenia, or personality disorder using self-declared data and prescriptions for antipsychotic medications from electronic health records. Subjects in the Psychiatric Genomics Consortium sample were assessed for MDD using a structured clinical interview. In the 23andMe sample, phenotypic status was based on responses to web-based surveys, with individuals that self-reported as having received a clinical diagnosis or treatment for depression classified as cases.

Bipolar Disorder (BP) — BP GWAS summary statistics were based on a GWAS meta-analysis of 57 studies from 21 countries in Europe, North America, and Australia, totaling 41,917 cases and 371,549 controls of European descent (Mullins et al., 2021). Cases were required to meet international consensus criteria (DSM-IV, ICD-9, or ICD-10) for a lifetime diagnosis of bipolar disorder (BD) established using structured diagnostic instruments from assessments by trained interviewers, clinician-administered checklists, or medical record review. Controls in most samples were screened for the absence of lifetime psychiatric disorders, as indicated. For five external cohorts, GWAS summary statistics for BD were shared with the PGC (iPSYCH, deCODE genetics, Estonian Biobank, HUNT, and UK Biobank). Cases in these cohorts were largely defined using ICD codes ascertained from medical records. All samples in previous PGC BD GWAS papers were included, and cohorts were added to the PGC in five waves (PGC11, PGC22, PGC PsychChip, PGC3 and External Studies).

Schizophrenia (SCZ) — SCZ GWAS summary statistics were based on a GWAS meta-analysis of 90 studies of European and East Asian ancestry, totaling 67,390 cases and 94,015 controls and 7,386 cases and 7,008 controls from 9 studies of African American and Latino ancestry (Trubetskoy et al., 2022). Samples were sub-grouped according to the following criteria: (1) Case definition: schizophrenia (SCZ), schizophrenia or schizoaffective disorder (SCZ/Schizoaffective), schizophrenia spectrum disorder, (2) Screened or unscreened controls for schizophrenia or other psychoses, (3) Recruitment setting: Cases recruited from Mixed (i.e., Community or Hospital setting), Community only, or Hospital plus ascertainment for clozapine treatment, and (4) Diagnostic strategy: Consensus diagnosis, research diagnostic interview, review of medical records, mixed strategy.

Attention-deficit/hyperactivity disorder (ADHD) — ADHD GWAS summary statistics were based on a GWAS meta-analysis of 12 studies in Europe, North America, and China, totaling 20,183 cases and 35,191 controls (Demontis et al., 2019). Psychiatric Genomics Consortium (PGC) case-status was defined by standardized diagnostic criteria and a population-based cohort of individuals with ADHD and controls from Denmark collected by the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH). Individuals with ADHD in iPSYCH were identified from the national Psychiatric Central Research Register and diagnosed by psychiatrists at a psychiatric hospital according to ICD-10.

Posttraumatic stress disorder (PTSD) — PTSD GWAS summary statistics were based on a GWAS meta-analysis of 60 studies in Europe, North America, and Africa, totaling 23,212 cases and 151,447 controls (Nievergelt et al., 2019). Phenotypic definitions ranged from clinically deeply characterized, small patient groups to large cohorts with self-reported PTSD symptoms. Trauma exposure included both civilian and/or military events, often with pre-existing exposure to childhood trauma, and the majority of controls were trauma-exposed.

Autism spectrum disorder (ASD) — ASD GWAS summary statistics were based on a GWAS meta-analysis of two studies (iPSYCH and PGC) in Europe and North America, totaling 18,382 cases and 27,969 controls (Grove et al., 2019). Cases were selected as those diagnosed with ASD in 2013 or earlier by a psychiatrist according to ICD-10 including diagnoses of childhood autism, atypical autism, Asperger's syndrome, other pervasive developmental disorders, and pervasive developmental disorders, unspecified. Five additional cohorts included in the PGC sample were assessed with standardized diagnostic criteria.

Tourette's syndrome (TS) — TS GWAS summary statistics were based on a GWAS meta-analysis of four studies in Europe, totaling 4,819 cases and 9,488 controls (Yu et al., 2019).

(1) GWAS1: Tourette diagnoses were assigned based on DSM-IV-TR criteria plus observation of tics by an experienced clinician. Controls were identified primarily from previously genotyped unselected population controls and ancestry matched to the cases. (2) GWAS2: Cases with DSM-V Tourette syndrome were identified by email/online recruitment combined with validated, web-based phenotypic assessments, or from Tourette syndrome specialty clinics. (3) GWAS2 FAM: The family sample consisted of probands and first-degree relatives with Tourette syndrome. Ancestry-matched controls were selected from a pool of previously genotyped controls. (4) TIC: Cases met criteria for either DSM-V Tourette syndrome or chronic motor or vocal tic disorder.

Anxiety disorders (ANX) — ANX GWAS summary statistics were based on a GWAS meta-analysis of the Million Veteran Program (MVP) which is an observational cohort study and mega-biobank in the Department of Veterans Affairs health care system, totaling 28,525 cases and 163,731 controls (Levey et al., 2020). Phenotypic assessment was based on a continuous score derived from the Generalized Anxiety Disorder 2-item scale. The scale asks, "Over the last 2 weeks, how often have you been bothered by the following problems?". 1. Feeling nervous, anxious, or on edge and 2. Not being able to stop or control worrying. Responses are based on the following options: Not at all (0), Several days (1), More than half the days (2), or Nearly every day (3). Total score is based on the sum of these two items and can range from 0-6.

Eating Disorders (ED) — ED GWAS summary statistics were based on a GWAS meta-analysis of 33 studies from 17 countries in Europe and North America, totaling 16,992 cases and 55,525 controls (Watson et al., 2019). Cases were generally defined from the various cohorts as those meeting diagnostic criteria for anorexia nervosa based on DSM-IV or ICD-10. Anorexia nervosa subtype phenotypes were dichotomized based on the presence or absence of binge eating. Anorexia nervosa with binge eating was defined as reporting ever (1) "Having eating

binges when you ate what most people would regard as an unusually large amount of food in a short period of time" and (2) "Having a sense of loss of control during those eating binges". Absence of binge eating was determined by a "No" response to either item. The no binge eating group had to also report no lifetime history of bulimia nervosa and no history of binge eating.

Obsessive-compulsive disorders (OCD) — OCD GWAS summary statistics were based on a GWAS meta-analysis of two previous GWAS of OCD (IOCDF-GC and OCGAS, 2018): (1) the International OCD Foundation Genetics Collaborative (IOCDF-GC) and (2) the OCD Collaborative Genetics Association Study (OCGAS), totaling 2,688 cases and 7,037 controls of European ancestry (IOCDF-GC and OCGAS, 2018). All cases met DSM-IV criteria for OCD. Screened controls from the Genomic Psychiatry Cohort were matched to OCGAS cases and controls from the IOCDF-GC GWAS were unscreened.

Alcohol dependence (AD) — AD GWAS summary statistics were based on a GWAS meta-analysis of 28 studies from Europe, North America, and Africa, totaling 11,569 cases and 34,999 controls (Polimanti et al., 2019). In brief, AD was defined as meeting criteria for a DSM-IV (or DSM-IIIR in one instance) diagnosis of AD and with the exception of three cohorts with population-based controls, all controls were screened for AD. Individuals with no history of drinking alcohol and those meeting criteria for DSM-IV alcohol abuse were additionally excluded as controls.

Cannabis use disorder (CUD) — CUD GWAS summary statistics were based on a GWAS meta-analysis of 20 studies in Europe and North America, totaling 17,068 cases and 357,219 controls (Johnson et al., 2020). PGC cases met criteria for a lifetime diagnosis of DSM-IV cannabis abuse or dependence derived from clinician ratings or semi-structured interviews. Cases from iPSYCH sample met ICD-10 codes for cannabis abuse or cannabis dependence or

both. deCODE sample cases met criteria for lifetime DSM-III-R or DSM-IV cannabis abuse or dependence or DSM-V cannabis use disorder. Controls were defined regardless of lifetime cannabis exposure across all datasets.

GWAS Summary Statistics for Non-Clinical Phenotypes

Problematic alcohol use (PAU) — PAU GWAS summary statistics were based on a GWAS meta-analysis of four studies of European ancestry with a sample size of 435,563 individuals (Zhou et al., 2020). MVP cases met diagnostic criteria for ICD alcohol dependence, PGC cases met diagnostic criteria for DSM-IV alcohol dependence, and UK Biobank population sample used scores derived from the AUDIT-P scale. The full AUDIT scale is comprised of two domains: alcohol consumption (AUDIT-C) and alcohol problems (AUDIT-P), including potential dependence on alcohol and experience of alcohol related harm. AUDIT-P includes: (1) "How often during the last year have you had a feeling of guilt or remorse after drinking?", (2) "How often during the last year have you been unable to remember what happened the night before because of your drinking?", (3) "Have you or someone else been injured because of your drinking?", and (4) "Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?".

Lifetime cannabis use (LCU) — LCU GWAS summary statistics were based on a GWAS meta-analysis of two studies of European ancestry with a sample size of 52,758 cases and 109,324 controls (Pasman et al., 2018). All subjects had self-report data available on whether the participant had ever used cannabis during their lifetime: Yes (1) versus No (0). Measurement instruments and phrasing of questions slightly differed across the subsamples included in ICC. UK Biobank, as part of an online follow-up questionnaire asked, "Have you taken cannabis

(marijuana, grass, hash, ganja, blow, draw, skunk, weed, spliff, dope), even if it was a long time ago?".

Drinks per week (DPW) — DPW GWAS summary statistics were based on a GWAS meta-analysis of 24 studies from Europe and North America with a sample size of 941,279 individuals (Liu et al., 2019). Subjects for the following three phenotypes were collected from many different cohorts (e.g., UK Biobank, deCODE, FinnTwin). Defined as the average number of drinks a participant reported drinking each week, aggregated across all types of alcohol. If responses were binned, the average was used. Reponses were based on the questions, "In the past week, how many alcoholic beverages did you have?" and "Thinking about the past year, on the average how many drinks did you have each week?".

Cigarettes per day (CPD) — CPW GWAS summary statistics were based on a GWAS meta-analysis of 25 studies in Europe and North America with a sample size of 337,334 individuals (Liu et al., 2019). Defined as the average number of cigarettes smoked per day, either as a current smoker or former smoker, and whether self-rolled or manufactured are smoked. For studies that collected a quantitative measure of cigarettes per day, the responses were binned as follows: 1 = 1-5, 2 = 6-15, 3 = 16-25, 4 = 26-35, and 5 = 36+.

Smoking initiation (SI) — SI GWAS summary statistics were based on a GWAS meta-analysis of 21 studies from Europe and North America with a sample size of 933,309 cases and 298,782 controls (Liu et al., 2019). This is a binary phenotype with any participant reporting ever being a regular smoker in their life (current or former) coded "2", while any participant who reported never being a regular smoker in their life coded "1". This was measured in the following few ways, (1) "Have you smoked over 100 cigarettes over the course of your life?",

(2) “Have you ever smoked every day for at least a month?”, and (3) “Have you ever smoked regularly?”.

Neuroticism (NEU) — NEU GWAS summary statistics were based on a GWAS meta-analysis of three studies in Europe and North America with a sample size of 523,783 individuals (Baselmans et al., 2019). In the UK Biobank, neuroticism was measured using the 12-item version of the Eysenck Personality Inventory Neuroticism scale. Questions include “Does your mood often go up and down?”; “Do you ever feel just miserable for no reason?”; “Are you an irritable person?”; “Are your feelings easily hurt?”; “Do you often feel fed-up?”; “Would you call yourself a nervous person?”; “Are you a worrier?”.

Extraversion (EXTRA) — EXTRA GWAS summary statistics were based on a GWAS meta-analysis of 29 studies of European ancestry with a sample size of 63,030 individuals (Van Den Berg et al., 2016). A harmonized latent extraversion score was estimated for all participants that were included in the GWAS meta-analysis. Extraversion item data came from the extraversion scales of the NEO Personality Inventory, the NEO Five Factor Inventory, the 50-item Big-Five version of the International Personality Item Pool inventory, the Eysenck Personality Questionnaire and the Eysenck Personality Inventory, the Reward Dependence scale of the Cloninger’s Tridimensional Personality Questionnaire, and the Positive Emotionality scale of the Multidimensional Personality Questionnaire.

Risk-taking (RISK) — RISK GWAS summary statistics were based on a GWAS meta-analysis of a single study from Europe with a sample size of 466,571 individuals (Linner et al., 2019). This measure, also referred to as general risk tolerance was determined in the UK Biobank using the following question, “Would you describe yourself as someone who takes risks?”. Possible responses include “Yes”, “No”, “Do not know”, and “Prefer not to answer”.

Methods

GenomicSEM

GenomicSEM is a flexible statistical R package which applies structural equation modelling to summary statistics comprising genetic variance-covariance and weight matrices. These variance-covariance and weight matrices are based on GWAS analyses of psychiatric disorders and non-clinical traits from partially overlapping samples. GenomicSEM is able to account for this overlap by estimating sampling covariances that indicate the extent to which the sampling distributions of the variance and covariance estimates co-vary with one another. This approach does not rely upon or analyze subject level data including individual SNP effects.

First, GWAS summary data are "munged" or standardized to ensure that all essential columns are present and syntactically correct for linkage disequilibrium score regression (LDSC). The munge function requires five pieces of information present in the summary statistic file: SNP rsID, A1 allele column indicating the effect allele, A2 allele column indicating the non-effect allele, logistic or continuous regression effect, p-value associated with effect. Once in the correct format, the munge function takes six arguments: summary statistic file names, name of the reference file (Hapmap 3 SNPs), trait names, sample sizes for each trait, INFO filter, and MAF filter. Default values for both filters were used (INFO > 0.9 and MAF > 0.01). INFO or the imputed information score is a measure of imputation quality for each SNP scaled from 0 to 1. MAF is the minor allele frequency. An MAF less than 0.01 classifies a particular variant as rare in the population. These two filters combined ensure that only high quality imputed and common SNPs are being used for analysis. Second, the multivariable LDSC is then run with five

arguments: munged file names, sample prevalences, population prevalences, a folder of LD scores used as the independent variable in LDSC (ld), and LDSC weights (wld). LDSC output consists of five objects: a covariance matrix (S), a sampling covariance matrix (V), a matrix of LDSC intercepts and cross-trait intercepts (I), heritability and co-heritability sample sizes (N), and the number of SNPs (M) used to compute the LD score. The sampling V matrix is used to correct for sample overlap between phenotypes.

Finally, a common factor model or user specified model can be tested using the genetic covariance matrix and a specification for the method of estimation either diagonally weighted least square or maximum likelihood. Once the model converges a R object with two elements is generated: Model$modelfit stores the model chi-square, degrees of freedom, p-value for the chi-square test, Akaike Information Criterion, Comparative Fit Index, and Standardized Root Mean Square Residual. Model$results stores the unstandardized and standardized results for each model using lavaan syntax to denote the relationships between estimated parameters.

Lavaan

The SEM approach is a powerful extension of path analysis (measuring only observed or manifest variables) that tests causal and non-causal relationships between observed and unobserved latent variables (Wright, 1920). Lavaan (Rosseel, 2012) allows users to fit a variety of latent variable models which include SEM, CFA, and latent growth curve models. The estimated models include both relative and absolute measures of model fit. Lavaan's syntax is user friendly and is centered around specifying the model based on the relationship among variables. Models are specified with a set of regression formulas. The tilde, "~", is the regression operator and a plus sign is used to separate independent variables. Here is a simple example of a regression formula with the dependent variable, y, on the left-hand side of the formula and the

independent variables separated by the "+" operator on the right-hand side: *y ~ x1 + x2 + x3 + x4*. If latent variables are included in the model, the user must "define" them as a function of their indicators. The special operator, "=~", is used for these definitions and can be read as "is measured by". For example, if a model includes three latent factors (f1, f2, f3) each with their own set of indicators the syntax might look as follows: *f1 =~ y1 + y2 + y3, f2 =~ y4 + y5 + y6, f3 =~ y7 + y8 + y9 + y10*. Variances and covariances are specified using a "double tilde" operator as follows: *y1 ~~ y1* (variance), *y1 ~~ y2* (covariance), *f1 ~~ f2* (covariance). Finally, intercepts for observed and latent variables are simple formulas with the intercept as the only predictor: *y1 ~ 1*, *f1 ~ 1*. In order to ensure that a model is properly identified, by default the first indicator has a fixed loading of 1 to scale the underlying factor(s) ("unit loading identification").

Analytic Procedures

Factor Analysis for Psychiatric Disorders

Factor analysis is a statistical technique used to describe observed variables and their covariance structure in terms of a smaller number of underlying latent or unobserved factors. Latent variables are constructs not directly measured but inferred from other variables in the dataset. Two different methods of factor analysis were implemented: confirmatory factor analysis (CFA) and exploratory factor analysis (EFA). Unlike EFA, CFA uses prior assumptions regarding the relationship between variables to inform the model structure. EFA and CFA (EFA being the predecessor to CFA) are encompassed under the umbrella term of SEM.

We began by testing 4 CFAs regarding the factor structure of the 12 psychiatric disorders (Table 1). In addition to the INT, EXT, and P (psychotic) factors, Model 1 includes an additional factor (disordered thinking, DT) comprising ASD, TS, and OCD.

The models are:

1) Model 1: Four factors indexed by the following indicators — INT =~ MDD + PTSD + ANX + ED, P =~ BPD + SCZ, EXT = ADHD + AUD + CUD, DT =~ ASD + TS + OCD
2) Model 2: Three factors in which ASD, TS, and OCD cross-load onto all factors — INT =~ MDD + PTSD + ANX + ED + ASD + TS + OCD, P =~ BPD + SCZ + ASD + TS + OCD, EXT =~ ADHD + AUD + CUD + ASD + TS + OCD (INT = internalizing, P = psychotic, EXT = externalizing)
3) Model 3: Three factors in which the factor loadings of ASD, TS, and OCD were fixed to zero — INT =~ MDD + PTSD + ANX + ED, P =~ BPD + SCZ, EXT =~ ADHD + AUD + CUD
4) Model 4: Same as Model 3 except indicators with a factor loading less than .3 were removed (ED) — INT =~ MDD + PTSD + ANX, P =~ BPD + SCZ, EXT =~ ADHD + AUD + CUD

The rationale for the model specifications of the first three models is based on the lack of an a priori hypothesis regarding how ASD, TS, and OCD fit into the factor structure of psychiatric disorders. Therefore, in Model 1 the three phenotypes constitute their own separate factor and in Model 2 the three phenotypes cross-load onto all three factors. In Model 3 the factor loadings of the three phenotypes were fixed to zero. Although there is not a consistent, objective threshold for retaining indicators in terms of their factor loading, some researchers consider a factor loading of .5 or greater to be sufficient, especially when dealing with smaller sample sizes. When sample size is considerably larger, as is true for the present case, generally a loading of .3 or

greater is considered acceptable for retaining indicators (Haig, 2005). Therefore, based on this post-hoc inspection, ED (.29) was removed from Model 4.

Factor Analysis for Psychiatric Disorders and Non-Clinical Phenotypes

Initially, the factor loadings for the psychiatric disorders were fixed to those estimated from Model 4 in Model A below. The non-clinical phenotypes were set to load onto the factors based on a priori relationships gathered from previous data cited in the literature. Therefore, the substance use traits, (problematic alcohol use, lifetime cannabis use, drinks per week, cigarettes per day, smoking initiation) loaded onto EXT. Risk-taking and extraversion were also hypothesized to load onto EXT as these traits are moderately correlated with substance use and are likely attributes of antisocial behavior. Furthermore, neuroticism, which is a rather complex facet of personality can be succinctly described as a deficit in emotional regulation characterized by excessive worry. Conceptually, this construct is closely associated with anxiety and the relatively broad scope that internalizing disorders encompass. Consequently, neuroticism can be reasonably modelled as loading onto INT. The factor loadings for the psychiatric disorders were freely estimated in Model B. Model B fit the data better than Model A. The only indicator with a factor loading less than .3 in Model B was extraversion and so it was fixed to zero in Model C.

The models are:

1) Model A: Psychiatric disorders are fixed to parameter estimates from Model 3 — INT =~ 0.85*MDD + 0.95*PTSD + 0.75*ANX + NEU, P =~ 0.85*BPD + 0.80*SCZ, EXT =~ 0.69*ADHD + 0.86*AUD + 0.77*CUD + EXTRA + RISK + DPW + PAU + CPD + SI + LCU

2) Model B: Psychiatric disorder factor loadings are freely estimated — INT =~ MDD + PTSD + ANX + NEU, P =~ BPD + SCZ, EXT =~ ADHD + AUD + CUD + EXTRA + RISK + DPW + PAU + CPD + SI + LCU
3) Model C: Extraversion factor loading is fixed to zero and the psychiatric disorders are freely estimated — INT =~ MDD + PTSD + ANX + NEU, P =~ BPD + SCZ, EXT =~ ADHD + AUD + CUD + RISK + DPW + PAU + CPD + SI + LCU

Model Comparisons

In GenomicSEM analyses, there is no one sample size because the GWAS studies on which the summary statistics are based vary in size and subject overlap. Therefore, when choosing the best fitting model, we were limited to fit indices that do not rely on sample size: the Akaike Information Criterion (AIC) (Akaike, 1974); Comparative Fit Index (CFI) (Bentler, 1990); Tucker Lewis Index (TFI) (Tucker & Lewis, 1973); and the Standardized Root Mean Square Residual (SRMR) (Hu & Bentler, 1999) to judge the best-fitting model. Both the CFI and TFI are incremental fit indices that penalize models with increasing complexity. CFI and TFI values closer to 1 indicate a better fit. The SRMR is an absolute measure of fit based on the difference between the observed and predicted correlations under each CFA model. A SRMR value of zero indicates a perfect fit. Finally, the pseudo-AIC is a comparative fit index, whereby a model with the lowest AIC values is interpreted as providing the optimal balance of explanatory power and parsimony.

Results

Genetic Correlations

Between Psychiatric Disorders

Genetic correlations (standardized variance-covariance matrices) from LDSC between all 12 psychiatric disorders are shown in Figure 5. Since the covariance structure remains unchanged when adding the 8 non-clinical measures, only a figure depicting the full trait covariance matrix is provided (Figure 5). MDD correlated highly with both ANX (r = 0.63) and PTSD (r = 0.74) and moderately correlated with BPD (r = 0.45) and ADHD (r = 0.42). The largest correlation among the psychiatric phenotypes was between ANX and PTSD (r = 0.95). Both psychotic disorders, SCZ and BP also correlated highly (r = 0.68). In contrast, correlations between MDD and SCZ, or between MDD and BP, ranged from r = 0.35 to 0.45, whereas the correlations between SCZ or BP and all other diagnoses were small to moderate (r = 0.09 to 0.41). OCD was moderately correlated with ED (r = 0.46) and TS (r = 0.43). The pattern of correlations is congruent with hypothesis 1; disorders falling along the same dimension correlate highly with each other (internalizing with internalizing, externalizing with externalizing, and psychotic with psychotic).

Between Psychiatric Disorders and Non-Clinical Phenotypes

Correlations between the psychiatric disorders and non-clinical phenotypes are also shown in Figure 6. Substantial covariation among the non-clinical behavioral phenotypes is present, particularly among substance use measures as well as between neuroticism and Internalizing disorders. Since neuroticism (NEU) was reverse scored along a "well-being spectrum" (Diener, 1984), negative correlation indicates an associated increase in NEU. In terms of correlations with Internalizing disorders, NEU correlates highly with MDD (r_g = -0.89). NEU also correlates

highly with two other Internalizing disorders, PTSD (r_g = -0.78) and ANX (r_g = -0.72). Correlations between the externalizing substance use phenotypes were large: CUD and AUD (r_g = 0.76), SI with CUD (r_g = 0.70) and AUD (r_g = 0.67). Moderate correlations are present with risk-taking: RISK and CUD (r_g = 0.47), LCU (r_g = 0.43), EXTRA (r_g = 0.40), ADHD (r_g = 0.37), and PTSD (r_g = 0.35). Although a correlation outside the bounds of -1 to 1 may seem impossible as is the case for PAU and AUD (r_g = 1.05), this observation is consistent with the instability of estimation for traits with considerable sample overlap or very small heritabilities, since the LDSC estimator is unbounded it is not entirely unreasonable to see out of bounds genetic correlation estimates if the true correlation is large (Visscher, 1998).

Figure 5. Correlation heatmap for 12 psychiatric disorders

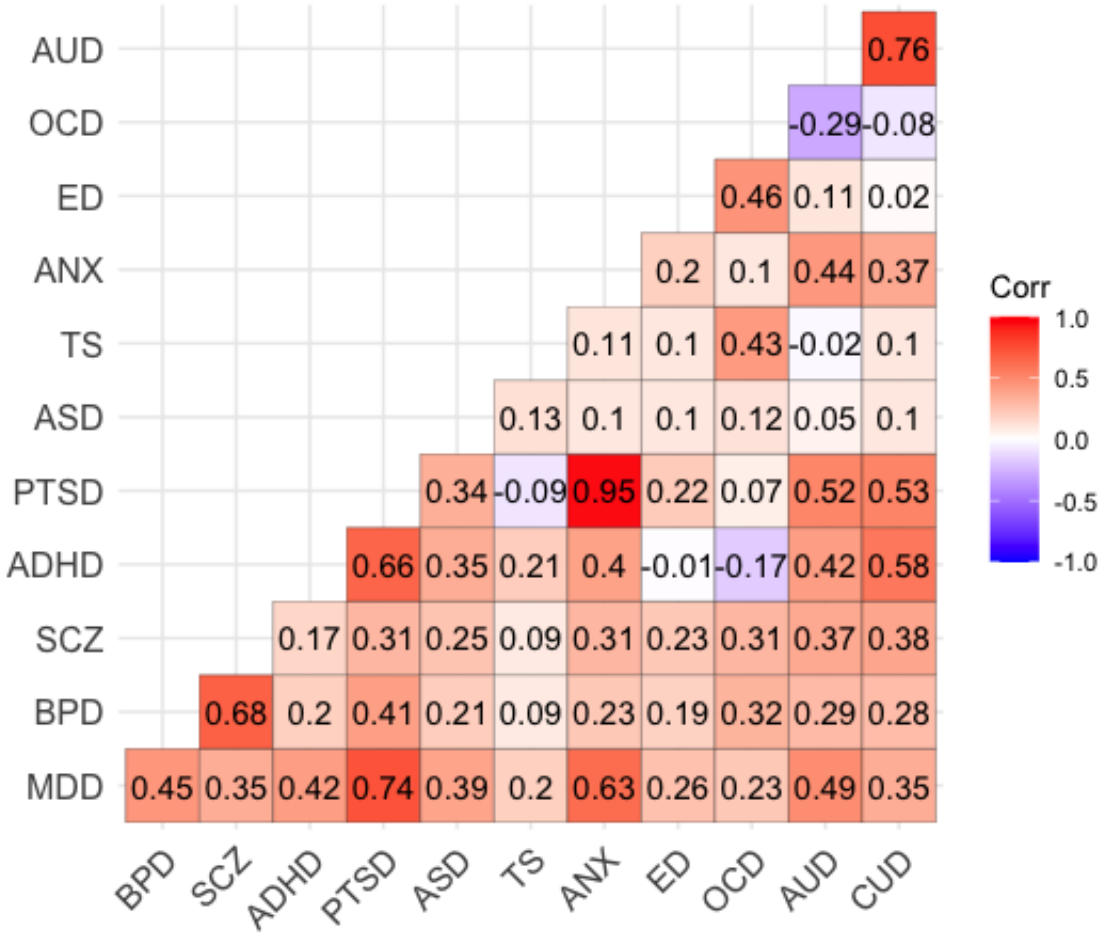
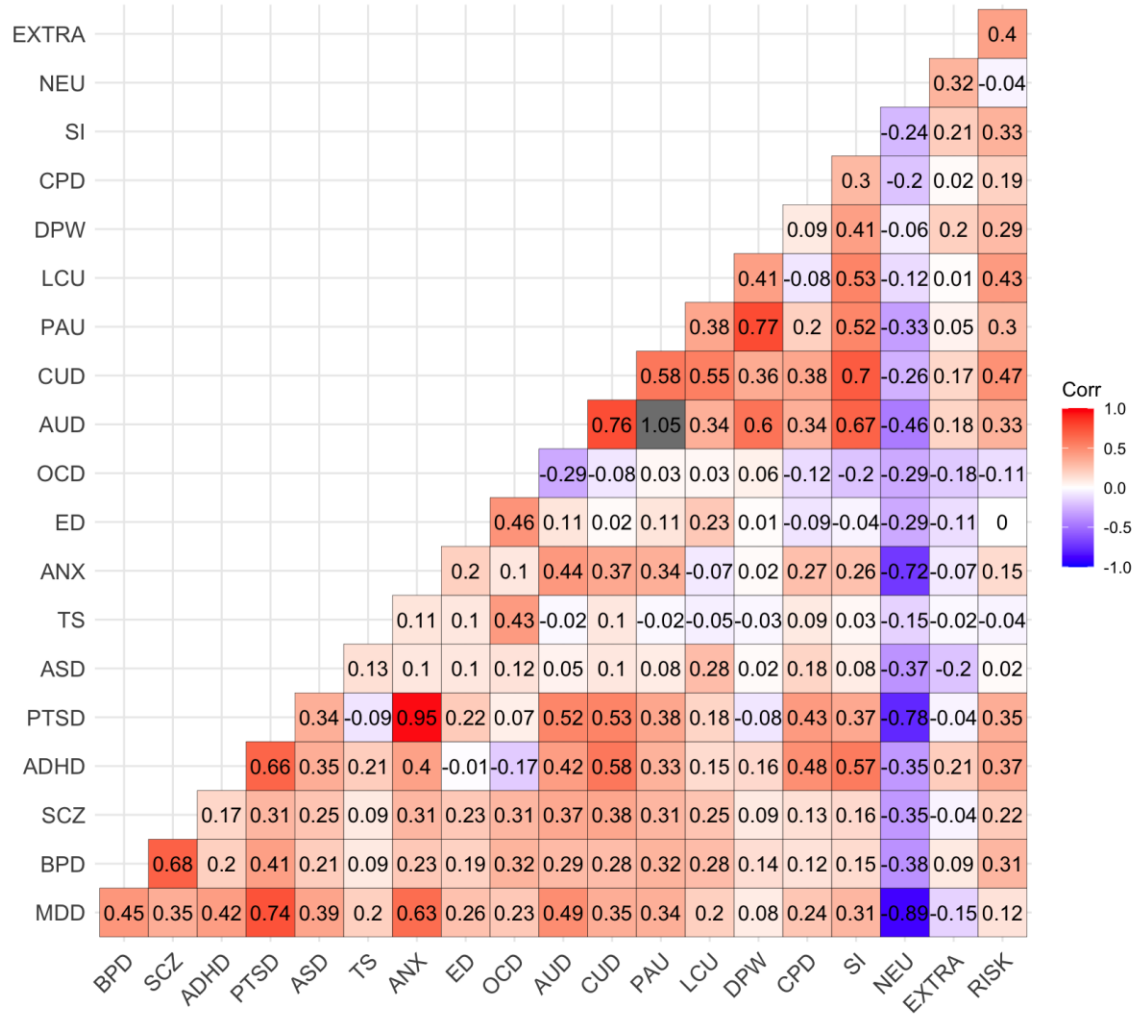


Figure 6. Correlation heatmap for 12 psychiatric disorders and 8 non-clinical phenotypes



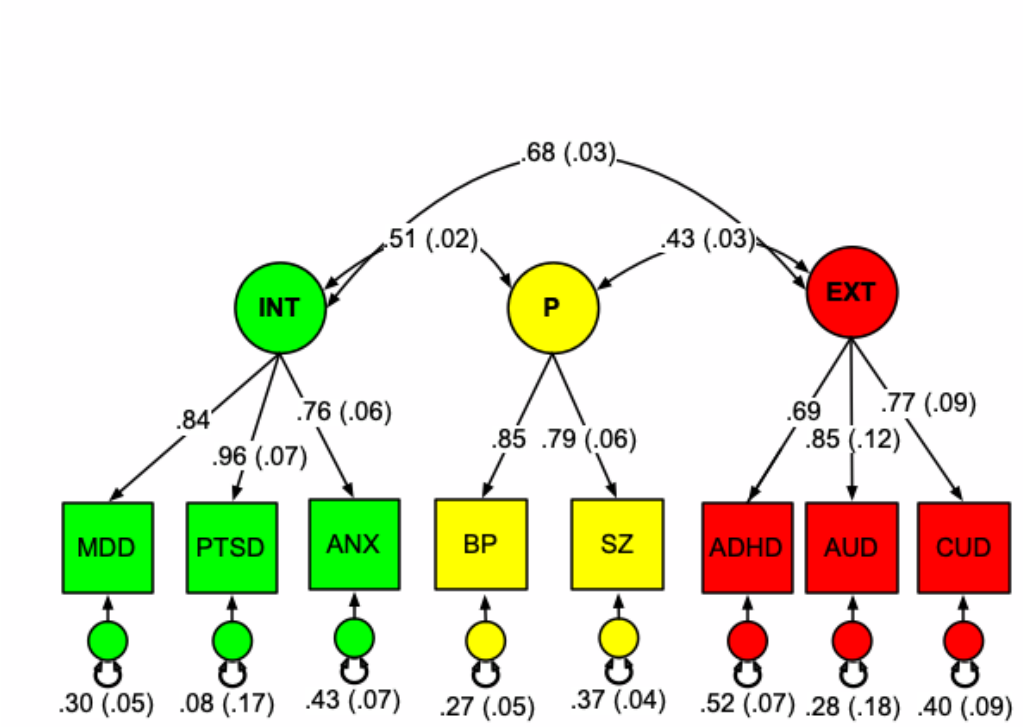
CFA of Twelve Psychiatric Disorders

Full model fit statistics for the 4 competing CFAs are shown in Table 2 below. The best fitting model is model 4 comprised of 3-factors with ASD, TS, and OCD factor loadings fixed to zero. Specifically, model 4 had a considerably smaller AIC, smaller chi-squared statistic, smaller SRMR, and larger CFI compared to models 1-3.

Table 2. Fit Statistics for Psychiatric Models

Models	chisq	df	p_chisq	AIC	CFI	SRMR
Model 1	528	48	5.82e-82	588	0.91	0.12
Model 2	458	45	8.94e-70	524	0.92	0.10
Model 3	182	24	2.79e-26	224	0.96	0.08
Model 4	120	17	1.77e-17	158	0.97	0.07

MDD, PTSD, and ANX all had high factor loadings on INT. BP and SCZ had high factor loadings on P. ADHD, AUD, and CUD had high factor loadings on EXT. All three factors were moderately correlated with each other: INT and EXT (r = 0.68), INT and P (r = 0.51), and EXT and P (r = 0.43). Complete factor loadings and factor correlations are included in the Model 4 figure below.



Model 4: Best Fitting Model for Psychiatric Disorders

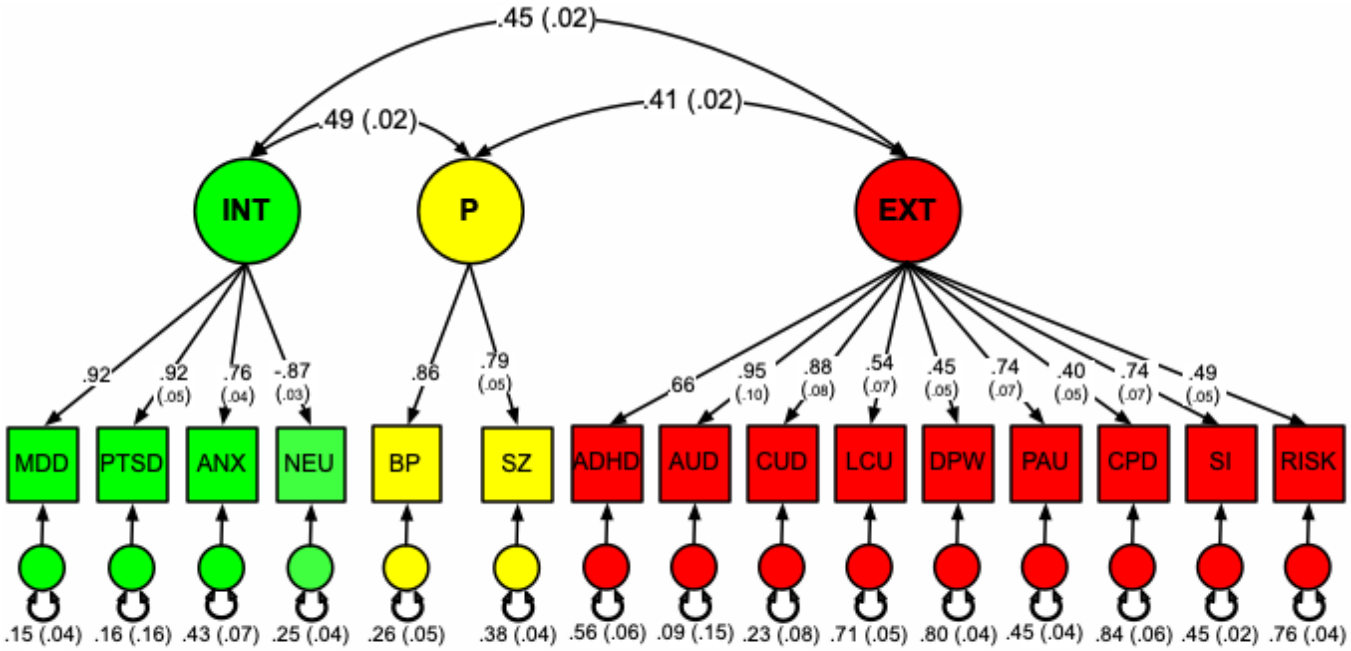
CFA of All Twelve Psychiatric Disorders and Eight Non-Clinical Traits

Model 4 served as the base model for the confirmatory factor analysis of all twenty phenotypes. Table 3 includes the full fit statistics for all models tested in the secondary CFA.

Table 3. Fit Statistics for Full Trait Models

Models	chisq	df	p_chisq	AIC	CFI	SRMR
Model A	21120	139	0	21184	0.69	0.14
Model B	8158	117	0	8230	0.80	0.13
Model C	5882	102	0	5950	0.81	0.13

Model C had the lowest AIC, largest CFI, and smallest SRMR of the three models that were tested. Complete factor loadings and factor correlations are included in the Model C figure below. The factor correlations were attenuated in the best fitting full model compared to the best fitting psychiatric model. The relative magnitudes of the factor correlations also changed (largest was between INT and P compared to the largest being between INT and EXT in the psychiatric model). Neuroticism loaded highly onto the INT factor (-.87). Non-clinical measures of substance use (lifetime cannabis use, drinks per week, problematic alcohol use, cigarettes per day, and smoking initiation) loaded moderately to highly onto the EXT factor. Additionally, risk-taking loaded moderately onto the EXT factor (.49).



Model C: Best Fitting Model for all Twenty Traits

Discussion

The objective of this study was to determine the factor structure of DSM psychiatric disorders based on molecular genetic data from the largest, publicly available GWAS summary statistics. Using genetic covariances based on twelve GWAS summary statistics for psychiatric disorders, three genetic factors were identified related to Internalizing, Externalizing, and Psychotic based disorders. The main analysis was expanded to include eight, non-clinical measures of substance use and personality. The same 3-factor structure was reproduced in the secondary analysis, confirming the validity of the latent constructs and their ability to capture the variance related to non-clinical measures of personality and behavior associated with clinical diagnoses.

Recent GenomicSEM studies provide partial corroboration with the present results, although different psychiatric disorders and phenotypes were modelled. A factor analysis of 11 psychiatric disorders (ADHD, problematic alcohol use, anorexia, ASD, ANX, BP, MDD, OCD, PTSD, SCZ, and TS) found that a correlated four factor model fit the data well (Grotzinger et al., 2022). Two of the four factors (compulsive, psychotic, neurodevelopmental, and internalizing) were recapitulated in the current results, Grotzinger et al. found an internalizing factor indexed by ANX and MDD and a psychotic factor indexed by BP and SCZ. The internalizing-psychotic factor correlation (.43) was similar to that modelled here (.49). Another factor analysis of six substance use phenotypes and five psychiatric disorders determined that a correlated two factor model explained the data (an externalizing factor indexed by three smoking phenotypes and ADHD and an internalizing-psychotic factor indexed by MDD, anorexia, BP, and SCZ) (Jang et al., 2022). A correlated four factor model best fit the data; however, it contained Heywood cases

(negative residual variance). This model was similar to the best fitting model described here with internalizing, externalizing, psychotic factors, and an additional substance use factor.

The moderate Externalizing-Psychotic correlation reiterates the partial but robust overlap between these two classes of disorders. Similarly, the Psychotic dimension was genetically related to the Internalizing dimension to a greater extent. The Externalizing-Psychotic factor correlation is consistent with another recent study using GenomicSEM in which the authors first estimated a common factor consisting of schizophrenia, cigarette smoking, and cannabis smoking (Song et al., 2022). In order to determine if this latent factor, SCZ_SMO, was related to other complex phenotypes, LDSC was applied to SCZ_SMO and psychiatric traits. SCZ_SMO was correlated with alcohol dependence ($r_g = 0.74$), lifestyle problems ($r_g = 0.83$), and number of sexual partners ($r_g = 0.60$). Abdellaoui et al., also found a positive factor correlation ($r_g = 0.28$) between a psychotic dimension indexed by schizophrenia and bipolar disorder and an all-encompassing psychiatric-substance use factor indexed by Tourette's, major depression, ADHD, autism, alcohol dependence, nicotine dependence, and cannabis use disorder.

Analysis here showed evidence for overlap in genetic liability for personality, substance use, and Internalizing disorders exhibited by the positive genetic correlations among neuroticism, major depression, alcohol use disorder, problematic alcohol use, and cannabis use disorder. This is also supported by Hatoum et al. (2022) reporting a positive correlation between neuroticism and addiction-risk factor ($r_g = 0.25$) as well as between compulsive disorders (Tourette's, OCD, eating disorders) and addiction-risk ($r_g = 0.32$).

Another notable result was the poor fit of extraversion in the final model. This is not necessarily surprising as other research has examined nuances related to extraversion or intermediate aspects of the trait, termed "communal extraversion" and "agentic extraversion".

Communal extraversion indexes the more well-adjusted aspect of the trait, namely, friendliness or gregariousness. Agentic extraversion, in contrast, is expressed as a tendency towards assertiveness, persistence, and achievement. In a principal component analysis, the authors used self-report measures of psychopathology that previously had been shown to be negatively or positively correlated with extraversion (Watson et al., 2019). The five-factor solution was comprised of Internalizing, Manic Narcissism, Externalizing, Dissociation, and Impulsive Inattentiveness domains. Comparable to the current study, communal extraversion was found to be negatively correlated with the Internalizing factor ($r = -.63$). Agentic extraversion correlated in the opposite direction with the Externalizing factor ($r = .10$). This same pattern was reflected across other measures of psychopathology included in the study. In other words, communal extraversion tends to be negatively correlated with psychopathology and agentic extraversion is positively related to psychopathology. This implies that the current definition of extraversion is overly simplistic and may explain why extraversion was dropped from the final model. Extraversion and other aspects of personality can be explained in more nuanced subcomponents (Strauss et al., 2016). Furthermore, extraversion had the smallest sample size of the eight non-clinical traits.

Overall, findings here support evidence from the literature suggesting that major DSM-based psychiatric disorders and related non-clinical personality and behavioral phenotypes are best described by a correlated three factor model. More broadly, these findings propose that psychiatric comorbidities are best explained by shared as well as unique genetic factors and non-diagnostic measures and they partially corroborate the large body of literature on psychiatric factor analysis in both twin and other phenotypic studies.

Limitations

Our results should be interpreted in the context of three main limitations. First, while most of the GWAS summary data were based on large, well-powered samples, TS and OCD in particular had sample Ns of less than 15,000 individuals each. Underpowered samples attenuate the probability of detecting true effects resulting in type II errors. This occurs when one fails to correctly reject the null hypothesis (effect size for each SNP is zero). More recent GWA studies are on the order of 100,000s of subjects (MDD and BP). Future studies that include updated GWAS data based on significantly larger samples may discover conflicting results compared to those found here. Additionally, GWAS included here were based on SNPs or common variants and did not include CNVs or other rare mutations. Mounting evidence suggests that rare variation explains a significant proportion of the variance in complex traits including psychiatric disorders (Wainschtein et al., 2022). A recent study examining the exomes of more than 100,000 cases and controls found that ultra-rare coding variants in ten genes conferred substantial risk for schizophrenia (odds ratios 3 – 50, $P < 2.14 \times 10^{-6}$) (Singh et al., 2022). These variants are expressed primarily in central nervous system neurons and include functions such as the formation, structure, and function of the synapse. Overlap of rare variant risk was detected between schizophrenia, autism spectrum disorders, epilepsy, and severe neurodevelopmental disorders. A recent approach termed DECO has been developed as an integrated method for rare variant and gene-set analysis (Nguyen et al., 2021). Compared to a method which only uses variant information, DECO is able to prioritize additional risk genes. More evidence for the possible role of rare genetic variants in psychiatric phenotypes was determined using a phenome-wide association study and gene-based burden tests for 37 psychiatric symptoms and disorders (Feng et al., 2022). There were suggestive associations of rare variation in PTEN with MDD,

KCNQ1 with substance addiction and disorders, APOB and PKP2 with tobacco use disorder, and DSC2 with alcoholism.

Second, samples were ethnically homogenous comprised of European ancestry raising the question in genetics about whether and to what degree the inclusion of more diverse ethnic populations will alter established patterns of findings. The results here may not apply to non-European populations. Recent emphasis has been placed on correcting underrepresentation of non-European ethnicities, specifically, African and Asian groups in genetic research (Peterson et al., 2019). Generalizability of key findings from medical research is important for personalized, actionable, and effective treatments which is the primary goal of medicine.

Third, the findings from this study warrant a cautious approach when interpreting and extrapolating them to subsequent research. The models did not yield satisfactory overall fits to the data, which raises concerns about their validity and generalizability. In particular, the Comparative Fit Index (CFI) and the Standardized Root Mean Square Residual (SRMR) fit indices deviated from the traditionally accepted benchmarks for a well-fitting model. A CFI value greater than 0.9 and an SRMR value less than 0.1 are typically deemed indicative of a good fit. The divergence of these indices from their respective thresholds suggests potential model misspecification or the presence of unaccounted variables. Researchers and practitioners should thus be circumspect when applying these findings and consider refining the models or incorporating additional variables in future studies.

Implications and Future Directions

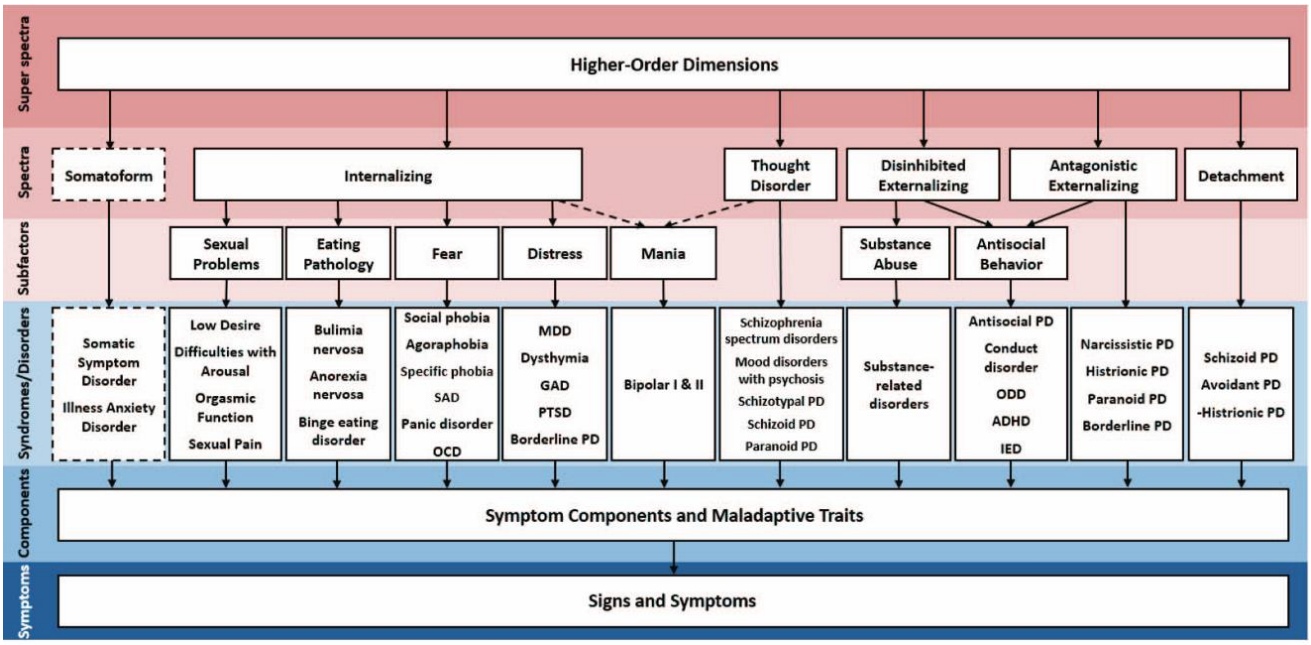
The relatively poor fitting models estimated here raise the ongoing problem in the field of psychiatric genetics regarding the accurate classification of psychiatric disorders and the elucidation of their etiologies. Although traditional frameworks which employ the categorical

classification of psychopathology (e.g., DSM and ICD) have received widespread acceptance in psychiatric practice, they are not without major limitations. Categorical classifications ignore comorbidity and developmental continuity between disorders (Caspi et al., 2020) and the underlying etiological and pathophysiological mechanisms that largely cut across diagnostic boundaries (Bzdok et al., 2018). Furthermore, DSM and ICD are not equipped to consider the extensive heterogeneity within each diagnosis and the overlap in symptoms across different diagnostic categories leading to difficulties with differential diagnosis and misdiagnosis (Fried, 2017) (Asherson et al., 2014). In response to these shortcomings, novel ongoing investigation has placed greater emphasis on attempts to incorporate constructs that are not based on standardized diagnostic criteria. One such initiative launched by The National Institute of Mental Health, the Research Domain Criteria project (RDoC), has posited that in order to establish a greater understanding of the etiology of psychiatric disorders research should begin with but not be limited to the assessment of symptoms (Insel, 2014). RDoC's proposed system integrates symptoms with both biological and psychosocial measures of disorders. Another related research approach adopting this framework has been referred to as the Hierarchical Taxonomy of Psychopathology (HiTOP) (Kotov et al., 2017). HiTOP, as its name suggests, organizes psychiatric disorders as dimensions that are related through multiple levels of a hierarchy (Figure 6). Signs and symptoms span the lowest, most specific level while an intermediate level consists of "spectra" or constellations of syndromes such as an internalizing spectrum indexed by fear, distress, eating pathology, and sexual problems subfactors. At the broadest level are "superspectra" which are composed of multiple spectra and represent a general factor of psychopathology, or the liability shared by all or most disorders.

RDoC and HiTOP share two core features: (1) Both recognize the limitations of traditional nosologies and emphasize the need for a dimensional approach to psychiatry and (2) both are designed to evolve with and integrate emerging evidence as a work-in-progress approach (Michelini et al., 2021). Despite their broad similarity, they also differ in a number of ways: (1) RDoC constructs were defined based on expert consensus regarding biobehavioral systems while HiTOP dimensions reflect a replicated empirical structure of psychopathology (2) RDoC places greater emphasis on the underlying pathophysiology or neurobiology, in contrast HiTOP focuses on the covariation among signs, symptoms, diagnoses, and maladaptive behaviors, and (3) RDoC has limited application in clinical practice and HiTOP while based on clinical interviews and observer reports does not account for the genetic and biological architectures that underpin psychiatric disorders (Michelini et al., 2021).

While the two approaches are clearly distinct, both systems could be integrated in a complimentary manner. Since RDoC currently has limited clinical utility, future RDoC research might use HiTOP to identify robust clinical targets. Similarly, RDoC could be integrated into future HiTOP research providing relevant information with regard to the etiological nature of disorders leading to a more comprehensive and biologically informed research paradigm.

Figure 6. HiTOP structure from Kotov et al. (2017)



Conclusion

This study aimed to determine the genetic factor structure observed in previous family, twin, and other phenotypic based studies between Externalizing, Internalizing, and Psychotic spectrum disorders using statistical methods that analyze GWAS-based correlations. The results showed that the previously established three-factor model for psychiatric disorders was confirmed (Internalizing, Externalizing, and Psychotic). Additionally, certain non-clinical traits such as substance use and risk-taking were found to be genetically related to Externalizing disorders, while high levels of neuroticism were associated with Internalizing disorders. These findings provide further insight into the genetic factors that underlie major psychiatric disorders and may have implications for the development of more accurate, genetically informed systems of psychiatric classification in the future.

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