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**Redefining Phenotypes to Advance Psychiatric Genetics: Implications
from Hierarchical Taxonomy of Psychopathology**

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Waszczuk, M. A. et al. (2018, June). *Redefining phenotypes to advance psychiatric genetics: implications from the Hierarchical Taxonomy of*

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General Scientific Summary

This study articulates a testable model that aligns the current understanding of genetic influences on psychopathology with observed patterns of co-occurrence among mental disorders. Specifically, it discusses the evidence that genetic influences do not fit traditional psychiatric diagnoses, and demonstrates that alternative classification approaches, such as the HiTOP model, can maximize precision and statistical power in the search for molecular genetic variants linked to mental illness.

Abstract

Genetic discovery in psychiatry and clinical psychology is hindered by suboptimal phenotypic definitions. We argue that the hierarchical, dimensional, and data-driven classification system proposed by the Hierarchical Taxonomy of Psychopathology (HiTOP) consortium provides a more effective approach to identifying genes that underlie mental disorders, and to studying psychiatric etiology, than current diagnostic categories. Specifically, genes are expected to operate at different levels of the HiTOP hierarchy, with some highly pleiotropic genes influencing higher-order psychopathology (e.g. the general factor), whereas other genes conferring more specific risk for individual spectra (e.g. internalizing), subfactors (e.g. fear disorders), or narrow symptoms (e.g. mood instability). We propose that the HiTOP model aligns well with the current understanding of the higher-order genetic structure of psychopathology that has emerged from a large body of family and twin studies. We also discuss the convergence between the HiTOP model and findings from recent molecular studies of psychopathology indicating broad genetic pleiotropy, such as cross-disorder SNP-based shared genetic covariance and polygenic risk scores, and we highlight molecular genetic studies that have successfully redefined phenotypes to enhance precision and statistical power. Finally, we suggest how to integrate a HiTOP approach into future molecular genetic research, including quantitative and hierarchical assessment tools for future data-collection and recommendations concerning phenotypic analyses.

Keywords: behavior genetics, comorbidity, general factor, molecular genetics, nosology, pleiotropy

Redefining Phenotypes to Advance Psychiatric Genetics: Implications from Hierarchical Taxonomy of Psychopathology

Psychiatric genetics promises to revolutionize our understanding of the neurobiology of mental illness and to inform drug development and personalized medicine approaches (Gandal, Leppa, Won, Parikshak, & Geschwind, 2016; Geschwind & Flint, 2015; Lester & Eley, 2013; Nelson et al., 2016). However, despite immense progress (Sullivan et al., 2017), genetic discovery in psychiatry remains hindered by shortcomings of phenotypic definitions, including diagnostic unreliability, comorbidity among disorders, and heterogeneity within them (Helzer et al., 2009; Kotov et al., 2017). The Hierarchical Taxonomy of Psychopathology (HiTOP) consortium proposed a data-driven classification system for a wide range of psychiatric disorders—based on a comprehensive review of existing nosologic and psychometric research—that addresses many of the shortcomings of traditional categorical diagnostic systems (Conway et al., 2018; Kotov, Krueger, & Watson, 2018; Kotov et al., 2017; Krueger et al., 2018). The HiTOP system promises to be a useful framework for psychiatric geneticists, who require valid and reliable phenotypes to maximize precision and statistical power in the search for genetic vulnerabilities to mental illness. Conversely, genetic findings are a crucial external validator of psychiatric nosology. The current paper discusses both issues: how the HiTOP model can inform future psychiatric genetic research by providing quantitative, hierarchically organized and easily implementable phenotypes, and how the HiTOP model dovetails with our existing understanding of the genetic architecture of psychopathology.

The HiTOP phenotypes - hierarchical and dimensional psychopathology

The HiTOP model organizes psychopathology into a *hierarchy*, in which each level captures a different degree of specificity with which mental illness is described (*Figure 1*). At the lowest level, the classification consists of individual maladaptive behaviors, symptoms and signs of illness. These can be aggregated into traits, such as compulsive checking or distractibility. At the next level, symptom components form dimensional syndromes, many of which are similar to existing diagnostic categories, such as obsessive-compulsive syndrome. The dimensional syndromes, in turn, form seven lower-order subfactors: distress, fear, sexual problems, eating pathology, mania, substance abuse and antisocial behavior. The subfactors, in turn, are organized into six higher-order spectra: internalizing, thought disorder, disinhibited externalizing, antagonistic externalizing, detachment, and somatoform. Finally, at the top of the hierarchy, there is a super spectrum, akin to a general factor of psychopathology (“p-factor”) (Caspi et al., 2014; Lahey et al., 2012; Lahey, Krueger, Rathouz, Waldman, & Zald, 2017). The proposed system is dynamic and flexible, as it accommodates updates as more structural data become available.

As detailed elsewhere (Kotov et al., 2017), HiTOP addresses two cardinal limitations of traditional classification systems, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). First, the hierarchical approach provides a way to flexibly accommodate heterogeneity by grouping related symptoms together and assigning unrelated symptoms to different components, while also making comorbidity an explicit and predictable feature of the model by classifying related components together. For example, the model posits that a syndrome (e.g. obsessive-compulsive disorder, OCD) will consist of homogenous components (e.g. checking, cleaning, and ritual compulsions), that it will be most closely associated with other syndromes from the subfactor to which it is assigned (i.e., fear subfactor), be

less closely associated with syndromes from other subfactors that belong to the same spectrum (e.g. distress, eating pathology, and sexual problems subfactors of the internalizing spectrum), and be even less closely associated with psychopathology from other spectra (e.g. substance abuse and antisocial behavior subfactors of the externalizing spectrum). The model also predicts that the proximity of these associations will be reflected in common risk factors, pathological processes, treatment responses, and illness course (Conway et al., 2018).

Second, the *dimensional* approach embodied in HiTOP frames mental health problems as continua, addressing many limitations of categorical classification, which include arbitrary boundaries between psychopathology and normality, diagnostic instability and inability to account for subthreshold cases. For example, the DSM-5 Field Trials have reported that 40% of diagnoses have not met even a relaxed cutoff for acceptable interrater reliability (Regier et al., 2013), although the same disorders often have evidenced excellent reliability when conceptualized dimensionally (Markon, Chmielewski, & Miller, 2011; Shea et al., 2002). Empirically-derived thresholds can be applied to dimensions in the HiTOP model to tailor them to specific clinical needs, such as screening or treatment decisions.

Hierarchical and quantitative genetic architecture - evidence from family and twin studies

There is ample empirical phenotypic evidence that psychopathology reflects the severe end of continuously distributed phenotypes (Krueger et al., 2018; Markon et al., 2011), indicating that quantitative phenotypes can be used to characterize clinical disorders in psychiatric genetic studies. First, a comprehensive review of taxometric research concluded that there is little support for discrete groups

within the continuously distributed internalizing and externalizing spectra, as well as normal and maladaptive personality, although the evidence was less conclusive for schizotypy and substance use (Haslam, Holland, & Kuppens, 2012). Second, studies using latent variable modelling approaches also generally find that dimensional models fit data better than categorical models, in particular for disorders from the internalizing and externalizing spectra (Aslinger, Manuck, Pilkonis, Simms, & Wright, 2018; Conway, Hammen, & Brennan, 2012; Eaton et al., 2013; Krueger, Markon, Patrick, & Iacono, 2005; Luo, Donnellan, Burt, & Klump, 2016; Wright et al., 2013), although there is also some evidence of discontinuity (Forbes, Baillie, & Schniering, 2016; Forbush & Wildes, 2017; Klein & Kotov, 2016). Individual symptoms have typically also been found to be continuous rather than binary (Flett, Vredenburg, & Krames, 1997; Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009).

In line with the phenotypic literature, biometrical studies have long demonstrated that genetic influences on psychiatric conditions operate in a dimensional fashion, reinforcing the conclusion that mental illness is better conceptualized in quantitative rather than categorical terms (Martin, Taylor, & Lichtenstein, 2017; Plomin, Haworth, & Davis, 2009). For example, Zavos et al. (2014) found that the same genetic factors influence severe and mild psychotic experiences in adolescents, indicating that quantitative genetic liability underpins a wide spectrum of psychotic symptoms. However, due to their traditional reliance on community samples, family and twin studies rarely encompass a sufficient number of participants with ascertained clinical diagnoses to directly test the genetic overlap between diagnoses and corresponding severity scores on a trait. Furthermore, some symptoms and diagnoses are too rare to study in typically-powered community samples. One

important exception is a recent study that demonstrated a common, highly heritable broad depression factor underpinning major depressive disorder (MDD) diagnosis, depression symptoms, and neuroticism trait, although MDD and neuroticism also showed substantial unique genetic effects (Kendler et al., 2018). Additional evidence of the dimensional nature of psychopathology comes from molecular genetic studies, as described in more detail in the next section.

Moreover, biometric models have provided compelling evidence of genetic overlap across traditional psychiatric phenotypes, informing psychiatric taxonomy (Lahey, Krueger, Rathouz, Waldman, & Zald, 2016; Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011; Martin et al., 2017; Rhee, Lahey, & Waldman, 2015; Smoller et al., 2018; South & DeYoung, 2013; Waldman & Slutske, 2000). The current paper builds on this body of evidence by explicitly relating it to a multi-tiered hierarchical organization that emerged from research on phenotypic structure. Specifically, in HiTOP, the super spectrum is hypothesized to capture genetic influences common across most psychiatric disorders (i.e. pleiotropy). At the next highest level, the genetic variance can either be retained or divided among different levels of specificity, depending on the analytic framework taken, see *Footnote 1* and Markon (2019). If the genetic variance is retained across the levels of the hierarchy, the six spectra reflect both common genetic influences, and influences specific to that spectrum. Additional genetic contributors emerge as one progresses down the hierarchy toward narrower dimensions, including specific traits and symptom clusters. If total genetic variance is divided into transdiagnostic and symptom-specific influences, e.g. using a bifactor approach, the genetic architecture of psychopathology is represented by independent sets of genes operating at different levels of specificity. Based on biometric modelling, the current review operationalizes etiological influences in a bifactor manner, unless stated otherwise. Accordingly, *Figure 2* summarizes the level of

empirical evidence for shared genetic influences at each level of the HiTOP hierarchy, herein referred to as genetic coherence. The key findings are described below, and a literature review is presented in *Supplement 1*.

Several twin and family studies provide evidence relevant to the super spectrum. Collective results from studies investigating shared genetic influences on symptoms from three or more higher-order spectra jointly indicate that a single common genetic factor plausibly contributes to all six spectra (Kendler, Aggen, et al., 2011; Pettersson, Larsson, & Lichtenstein, 2016). For example, a Swedish national study of >1.5 million siblings identified a general genetic factor influencing diagnoses from the thought disorder, externalizing, and internalizing spectra, accounting for between 10% (for ADHD) to 36% (for drug abuse) of the total observed phenotypic variance in these diagnoses (Pettersson et al., 2016). Findings also included two sets of genetic influences independent of the general factor, one specific to thought disorder (accounting for 31% of the phenotypic variance in schizophrenia, 45% in schizoaffective disorder, and 16% in bipolar disorders), the other to the internalizing and externalizing spectra (ranging from 6% of the phenotypic variance explained for MDD to 42% for drug abuse), suggesting that the latter two dimensions were genetically more similar to each other than to the thought disorder spectrum. A second study of 2,111 Norwegian twins identified moderately correlated ($r=.16-.49$) internalizing, disinhibited externalizing, antagonistic externalizing, and detachment genetic dimensions (Kendler, Aggen, et al., 2011). Although an overall higher-order general factor was not explicitly examined, the pattern of genetic correlations among the extracted spectra suggests that a degree of common genetic vulnerability to all disorders is likely.

When several disorders or symptoms belonging to a particular HiTOP spectrum (e.g. internalizing, disinhibited externalizing) are modeled jointly, a

common genetic factor underpinning all of them typically emerges. For example, one study assessed antisocial behavior, conduct disorder, and drug, nicotine, and alcohol dependence in a sample of 1,999 biological and adoptive families, and identified a highly heritable disinhibited externalizing spectrum that captured a high proportion of the genetic influences on the five disorders (i.e. 61% of phenotypic variance in the latent externalizing factor was due to genetic influences), indicating genetic coherence of this spectrum (Hicks, Foster, Iacono, & McGue, 2013). The spectra are also genetically distinct, in that conditions belonging to the same spectrum share more genetic variance than conditions from different spectra. Nonetheless, spectra that are most frequently studied together, internalizing and externalizing, show a substantial genetic overlap (Cosgrove et al., 2011; Hink et al., 2013; Kendler & Myers, 2014; Kendler, Prescott, Myers, & Neale, 2003; Wolf et al., 2010), and developmental studies have found evidence for a single genetic factor influencing both internalizing and externalizing disorders (Ehringer, Rhee, Young, Corley, & Hewitt, 2006; Spatola et al., 2007). For example, Spatola et al. (2007) found that a common genetic factor accounted for 36-45% of total phenotypic variance of individual Child Behavior Checklist scales measuring internalizing and externalizing symptoms. Moreover, bifactor analyses that modeled an overarching general factor alongside specific internalizing and disinhibited externalizing dimensions have found that although the general factor explains most of the heritability of internalizing and externalizing problems, a significant proportion of genetic variance remained that was specific to the internalizing and externalizing spectra (Lahey et al., 2011; Mikolajewski, Allan, Hart, Lonigan, & Taylor, 2013; Tackett et al., 2013; Waldman, Poore, van Hulle, Rathouz, & Lahey, 2016).

At the level of subfactors, studies support independent genetic influences on fear, distress and substance abuse subfactors that emerge alongside higher-order factors (Hettema, Prescott, Myers, Neale, & Kendler, 2005; Kendler et al., 2003; Kendler et al., 1995; Waszczuk, Zavos, Gregory, & Eley, 2014). For example, in a sample of 1,549 young adult twins, a genetic fear subfactor influencing panic disorder, separation anxiety and social phobia symptoms was derived, accounting for 6-15% of total heritability of these symptom dimensions, and was independent of overarching internalizing genetic influences shared with depression and generalized anxiety symptoms, that accounted for over half (63-85%) of the total heritability of each symptom dimension (Waszczuk et al., 2014). Finally, both eating pathology and antisocial behavior subfactors demonstrate subfactor-specific genetic influences (Bornovalova, Hicks, Iacono, & McGue, 2010; Bulik et al., 2010; Cosgrove et al., 2011; Hink et al., 2013; Lahey et al., 2011; Mikolajewski et al., 2013; O'Connor et al., 2016; Tuvblad, Zheng, Raine, & Baker, 2009), but it remains unclear whether genetic factors underpinning these subfactors are independent of influences on higher-order spectra because in many of these studies higher levels of the hierarchy have not been modelled.

Twin studies have begun to investigate genetic influences on individual syndromes, symptom components, and maladaptive traits. Previous studies investigated genetic influences underpinning narrow symptom components of depression (Kendler, Aggen, & Neale, 2013), OCD (Iervolino, Rijdsdijk, Cherkas, Fullana, & Mataix-Cols, 2011), ADHD (McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007; Nikolas & Burt, 2010), aggression (Coccaro, Bergeman, Kavoussi, & Seroczynski, 1997; Vernon, McCarthy, Johnson, Jang, & Harris, 1999) and antisocial personality (Kendler, Aggen, & Patrick, 2012; Rosenström et al., 2017), finding that some genetic influences operate at the level of the overarching

syndrome, whereas other genetic influences are specific to individual symptom components. For example, while there was a common genetic factor influencing five symptom components of OCD - checking, hoarding, obsessing, ordering, and washing, accounting for 20-35% of total phenotypic variance - the first four OCD components also showed independent genetic influences that accounted for 11-23% of total phenotypic variance (Iervolino et al., 2011).

Finally, non-shared environmental influences (i.e., those uniquely experienced by only one co-twin or sibling) can be modeled using family and twin data. Non-shared environmental influences are typically disorder-specific and contribute to the distinction among psychiatric conditions, as described in more detail in *Supplement 2*. Nonetheless, some environmental influences contribute to the coherence of higher-order HiTOP spectra, such as internalizing (Hettema, Neale, Myers, Prescott, & Kendler, 2006; Hettema et al., 2005; Mosing et al., 2009), externalizing (Bornovalova et al., 2010; Krueger et al., 2002; Tuvblad et al., 2009), thought disorder (Cardno et al., 2012) and somatoform (Kato, Sullivan, Evengård, & Pedersen, 2009) spectra, although they account for considerably less common variance in those phenotypes than higher-order genetic factors. For example, in a study of >30,000 Swedish twins, non-shared environmental influences constituted about one-third of influences on a general factor underpinning symptoms of depression, generalized anxiety, and four somatoform syndromes (chronic widespread pain, chronic fatigue, irritable bowel syndrome, and recurrent headache), and about one-half of influences on an independent somatoform spectrum (Kato et al., 2009).

Hypotheses and future directions for quantitative genetics

Taken together, the existing behavior genetic literature indicates that the HiTOP model may be well aligned with the genetic architecture of psychopathology observed by family and twin studies. It suggests that key features of the HiTOP

hierarchy, which were largely derived from psychometric modeling, could be genetically coherent (*Figure 2*). Nonetheless, the phenotypic structure hypothesized by the HiTOP model should be tested directly using confirmatory structural twin modelling and adjudicated where possible using fit statistics, in order to rigorously assess the degree of alignment between the phenotypic and genetic architecture of psychopathology. In particular, genetically informed structural analyses are needed to confirm the hypothesized genetic structure of several understudied aspects of psychopathology, such as the detachment spectrum and sexual problems subfactor. Furthermore, using identified or hypothesized phenotypic structures as a starting point for comparing different models of higher-order genetic influences in a confirmatory manner might bias phenotypic and genetic literatures towards convergence. Therefore, hypothesis-free, exploratory analyses of genetic correlations should also be conducted, akin to the approach taken by Kendler, Aggen, et al. (2011). In case genetic models derived from HiTOP organization are not confirmed, alternative structural models derived directly from genetic data would be able to inform future genetic research as well as influencing future revision of phenotypic models. Indeed, such findings could challenge relevant aspects of the HiTOP model and accordingly lead to revisions of the model.

From a study design perspective, achieving these goals would be facilitated by the inclusion of more comprehensive, transdiagnostic assessments across the full spectrum of severity, ranging from relevant personality traits to severe clinical problems. From an analytic perspective, it will be useful to focus on measuring and modeling the genetic structure of the lower-order dimensions (symptom components and maladaptive traits) to build a truly bottom-up model. Ultimately, a twin study of the full HiTOP model is needed to test the genetic architecture of psychopathology comprehensively, ideally at multiple levels of

the hierarchy simultaneously. Finally, the nature of the phenotypic general factor remains debated, with some suggestions that it reflects traits that nonspecifically increase the general risk for psychopathology and others raising the possibility that it captures distress or impairment common to all psychiatric illness (Caspi & Moffitt, 2018; Oltmanns, Smith, Oltmanns, & Widiger, 2018; Waldman et al., 2016). Etiologic hypotheses regarding the general factor can be evaluated empirically, for example by testing whether there are significant genetic and environmental correlations between the general factor and measured negative affect, functional impairment, and other psychosocial and environmental variables (Tackett et al., 2013; Waldman et al., 2016).

Molecular genetic studies - evidence for transdiagnostic genetic pleiotropy

The field of molecular psychiatric genetics has made enormous advances in the last decade. For example, case-control genome-wide association study (GWAS) meta-analyses conducted by the Psychiatric Genomics Consortium (PGC) led to identification of >150 independent genetic associations reaching genome-wide significance for schizophrenia, 30 for bipolar disorder and 12 for ADHD (Stahl et al., 2017; Sullivan et al., 2017), with findings even higher when combined with other datasets, e.g. a total of 102 significant hits for depression (Howard et al., 2018). These studies have also demonstrated a quantitatively distributed polygenetic liability to mental illness, on a continuum from trait variation in the general population to corresponding clinical diagnoses (Martin et al., 2017; Sullivan et al., 2017). Beyond notable disorder-specific findings, molecular genetic studies have also informed the transdiagnostic genetic architecture of psychopathology (Gizer, 2016; Santoro et al., 2016; Smoller, 2013; Smoller et al., 2018; Wray et al., 2014). The overarching pattern of findings from GWAS indicates widespread pleiotropy, with many genes and individual variants

influencing more than one disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013b; Serretti & Fabbri, 2013; Sivakumaran et al., 2011).

Use of polygenic risk score (PRS) methodology allows for an examination of the prediction of phenotypes using millions of genome-wide common variants, and also shared common variant genetic covariance across disorders and traits. This has perhaps been the most informative methodology for understanding latent genetic architecture and real-world prediction of traits, though like with other molecular genetic studies, this work has been limited by the depth and breadth of the phenotypes being studied. Several reports on PRSs have informed etiology in the last decade. For example, a PRS for smoking has been observed to be associated with alcohol and cannabis use ($R^2=0.4-1.5\%$) (Vink et al., 2014), in line with common genetic influences on various forms of substance abuse. Other work has found a PRS for ADHD to be significantly associated with comorbid conduct disorder symptoms, with $R^2= 1.1\%$ higher in comorbid than pure ADHD cases (Hamshere et al., 2013), consistent with a broader externalizing spectrum. In the internalizing domain, a PRS for depression was also associated with anxiety, explaining about 2.1% of variance in anxiety (Demirkan et al., 2011). Finally, a PRS for schizophrenia was associated with nicotine use, depression and anxiety symptoms, and family history of depression, anxiety, alcohol use disorder and drug use (Docherty et al., 2017), which is in line with broad genetic risk for psychopathology. Consistent with broad influences of PRS, a recent study found that PRSs for schizophrenia and neuroticism were associated with a general factor of psychopathology in adolescence ($\beta=.06$ and $.07$, respectively), with little evidence for disorder-specific associations (Jones et al., 2018). In sum, PRSs appear to capture largely transdiagnostic genetic influences on phenotypic presentation, with uncertain

specificity of the polygenic signal when applied to categorical phenotypes in isolation.

Studies investigating common variant SNP-based bivariate genetic correlations have also revealed patterns of genetic overlap that inform our understanding of the genetic architecture of psychopathology and are consistent with the HiTOP organization. For example, one PGC study found that bipolar disorder showed the highest SNP-based genetic correlation with schizophrenia ($r_g=.68$), and a considerable correlation with depression ($r_g=.47$) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013a), and another study reported a genetic correlation between bipolar disorder and anorexia nervosa ($r_g=.16$) (Lo et al., 2016), which accords with bipolar disorder's position within both the thought disorder and internalizing spectra in HiTOP (*Figure 1*). This pattern of results has been reported in data from non-PGC sources (Wang, Gaitsch, Poon, Cox, & Rzhetsky, 2017), as well as in a recent gene expression investigation (Gandal et al., 2018). The latter study found the highest transcriptome correlation between bipolar disorder and schizophrenia ($r_t=.70$), with both disorders also showing significant, albeit smaller, transcriptome overlap with depression ($r_t=.25$ and $.30$, respectively). Recent work has also identified very high SNP-based genetic overlap between depression, mood and anxiety disorders (Wang et al., 2017), supporting genetic coherence of the internalizing spectrum. Another study created a SNP-based genetic correlation matrix comprising a number of phenotypes related to substance use and found a pattern of correlations indicating the presence of substance specific genetic effects, as well as high genetic overlap between use of different types of substances (e.g. $r_g=.83$ between cannabis initiation and smoking initiation, $r_g=.44$ between nicotine and alcohol consumption) (Nivard et al., 2016), which supports genetic coherence of the substance abuse subfactor. Finally, several

studies have revealed genetic correlations between disorders from different higher-order spectra, which is in line with the overarching genetic pleiotropy that may indicate a general factor of psychopathology (Anttila et al., 2018; Bulik-Sullivan et al., 2015; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013a; Lo et al., 2016; Selzam, Coleman, Moffitt, Caspi, & Plomin, 2018; Wang et al., 2017). Nonetheless, it is also important to note that not all phenotypes showed significant PRS or SNP-based genetic correlations, and it is unclear whether these results point to low genetic overlap, or are a result of low discovery GWAS sample sizes for some conditions (i.e. PTSD).

How HiTOP phenotypes can facilitate genetic discovery

Despite enormous progress, molecular genetic discovery in psychiatry has been dependent on categorical, case-versus-control analyses embedded within traditional diagnostic classification systems. The HiTOP model endeavors to refine this phenotypic framework and accelerate genetic discovery in two major ways. First, the hierarchical approach provides alternative, empirically-validated phenotypic targets of genetic inquiry. Specifically, the model allows genetic studies to address problems associated with comorbidity by focusing on major dimensions underlying numerous psychiatric conditions, and to reduce issues associated with within-disorder heterogeneity, by focusing on well-characterized tight-knit lower-order dimensions (Hodgson, McGuffin, & Lewis, 2017; Mullins & Lewis, 2017; Van Der Sluis, Verhage, Posthuma, & Dolan, 2010). Currently, when a new genetic variant is significantly associated with (or PRS is created for) a particular disorder (e.g. MDD), it is uncertain whether it indicates risk for a particular symptom within this condition (e.g. anhedonia), or for a higher-order spectrum to which that condition belongs more broadly (e.g. the internalizing spectrum) (Gatt, Burton, Williams, & Schofield, 2015; Hettema, Chen, Sun, & Brown, 2015; Serretti & Fabbri, 2013). Furthermore, extensive heterogeneity

within traditional diagnoses likely obscures links with symptom-specific genetic variants and therefore large samples are needed to find relations between these variants and diagnoses (Manchia et al., 2013; Wray & Maier, 2014). Using HiTOP phenotypes with a known placement within the hierarchy can resolve these concerns, and enable genetic studies to choose phenotypic targets of the specific breadth that the study aims to investigate, e.g. an internalizing spectrum, distress subfactor, or anhedonia component. Indeed, differential discovery expected to emerge at each level of the phenotypic structure, and the HiTOP model provides tools for explicating this architecture systematically. As such, the HiTOP model can increase the statistical power and precision of genetic research by providing internally consistent phenotypic targets at every level of the hierarchy. Specifically, power analyses demonstrate that optimized phenotypic modelling will appreciably increase power to detect genetic effects over the use of total scores (Van Der Sluis et al., 2010).

Second, the quantitative approach supported by the HiTOP model may increase statistical power for genetic discovery. As discussed above, quantitative phenotypes better capture illness severity and characterize subthreshold cases than categorical diagnoses (Markon et al., 2011; Shea et al., 2002). The loss of this information when using categorical diagnoses can weaken the genetic signal, for example when subthreshold cases are included in the control group or when diagnosis changes over time (as misclassification between cases and non-cases and between cases of different disorders is quite common even in well-designed studies) (Bromet et al., 2011; Moffitt et al., 2010). The HiTOP model allows for thresholding when it is pragmatically useful, but does not require it. Furthermore, HiTOP avoids concerns regarding the selection of healthy controls. Contrasting healthy controls and cases with a clinical diagnosis has significant limitations (Preacher, Rucker, MacCallum, & Nicewander, 2005; Sher & Trull,

1996; Uher & Rutter, 2012). In particular, healthy controls and clinical cases typically differ on characteristics unrelated to the psychopathology of interest, such as intelligence, socio-economic status, and co-occurring mental health symptoms, which can conflate estimates of genetic influences and genetic associations among disorders. In addition, diagnostic misclassification inflates genetic correlations (Kendler, Chatzinakos, & Bacanu, 2019; Wray, Lee, & Kendler, 2012). Instead, samples from a single population with a dimensional assessment of symptom severity (e.g., a representative community sample or unselected group of patients seeking mental health services) are generally easier to obtain and allow for more precise and clinically useful estimates of effect size.

Quantitative phenotypes enhance statistical power, with power analyses demonstrating that continuous phenotypes yield more power over categorical diagnoses in GWAS under many conditions (Van der Sluis, Posthuma, Nivard, Verhage, & Dolan, 2013; Van Der Sluis et al., 2010; Yang, Wray, & Visscher, 2010). Specifically, case-control designs have advantageous power when as many cases as controls are recruited under the condition of low disease prevalence, but if the sample is representative of the population, quantitative phenotypes yield higher power. Notably, it is often difficult to recruit sufficiently large samples with “rare” disorders to meet power requirements of case-control design. Finally, quantitative approaches can identify non-linearity in genetic influences, and thus can indicate whether certain aspects of psychopathology are indeed better represented as categories (rather than assuming that to be the case), and can inform optimal thresholds for such classifications (Plomin & Kovas, 2005). This has been empirically tested in twin studies, with overwhelming evidence for continuity of etiological influences across symptom severity (Martin et al., 2017; Plomin et al., 2009). Nonetheless, discontinuities in

etiology have also been demonstrated, for example, one twin study found that the extreme low end of the ADHD spectrum has a different genetic etiology from higher levels of ADHD symptoms, suggesting that low ADHD might reflect different genetic influences (Greven et al., 2016).

Hypotheses and novel phenotypic approaches in molecular genetic studies

Hypotheses and molecular evidence relating to the hierarchical structure.

Although the existing literature suggests that it will be possible to identify genetic vulnerabilities associated with different levels of the HiTOP hierarchy, predictions of this model should be directly tested in molecular genetic studies. Specifically, the model posits a set of testable hypotheses that would organize and encourage the exploration of the interface between phenotypic and molecular genetic studies. First, different genetic findings are hypothesized to emerge at different levels of the HiTOP hierarchy. For example, if the phenotype was first partitioned using a bifactor model into variance specific to the general factor, spectrum, subfactor etc., and GWASs were conducted to identify genetic hits associated with each level, the model predicts (1) that genetic variants will be identified at each level, and (2) that different, non-overlapping genes will be identified at each level. The same two predictions hold for PRS built for these phenotypes, and for associated downstream biological pathways. As such, a higher-order approach to phenotypes may increase the precision of genetic findings, differentiating between genetic liability for broad psychopathology and dimension-specific genetic risk factors. One implication of such genetic findings is that they might inform Mendelian randomization studies (Pingault et al., 2018) by providing more precise and less pleiotropic instrumental variables (e.g. PRS scores) for psychiatric predictors.

Furthermore, the HiTOP model makes specific predictions about the pattern of genetic correlations. Specifically, the HiTOP model hypothesizes that dimensions within the same spectrum (or subfactor) will show stronger common variant SNP-based genetic correlations than dimensions assigned to different spectra or subfactors. For example, the HiTOP model predicts that worry may have higher genetic correlations with depression and traumatic re-experiencing than with interaction anxiety, which in turn will be larger than the genetic correlation of worry with callousness.

Predictions about general and specific genetic vulnerabilities have been supported by molecular genetic evidence. A recent study found that a genetic general factor of psychopathology, derived using principal component analysis of genetic correlation matrices from three different molecular methods (Genome-wide Complex Trait Analysis, Linkage-Disequilibrium Score Regression, and PRS correlations), accounted for 19-57% of all genetic variance for a range of psychiatric traits (Selzam et al., 2018). While this finding demonstrates that a significant proportion of genetic variance is captured by the general factor, the remaining, in some cases, even larger proportion of genetic variance is captured at lower levels of the hierarchy. This has been tested more formally by applications of genomic structural equation modeling (genomic SEM), which extracts common genetic dimensions from bivariate genetic associations (Grotzinger et al., 2018). The first study to use this approach suggested that while many genes broadly influence liability to numerous psychiatric disorders, other genetic factors remain disorder-specific, mirroring the hierarchical structure from phenotypic and twin modelling literatures (Grotzinger et al., 2018). Another study using the genomic SEM method has modelled the intermediate level of the hierarchy and found support for correlated internalizing, externalizing, and thought disorder spectra (Luningham, Poore, Yang, &

Waldman, 2018). As the matrix of genetic correlations expands, genomic SEM will allow further evaluation of the alignment between genetic architecture and the HiTOP model.

Hypotheses and molecular evidence relating to redefined phenotypes.

Direct comparison of the number of SNPs identified using dimensional and hierarchical phenotypes vs. DSM-based disorders serves as a more direct test of the hypothesis that the model has incremental utility for genetic studies. We hypothesize that HiTOP phenotypes will help to identify a higher number of genetic variant effects. Already, some molecular genetic studies have begun using the approach of combining individual phenotypes to form higher-order spectra (Lee et al., 2016; McGue et al., 2013; Neumann et al., 2016; Otowa et al., 2016; Xu et al., 2015). For example, a meta-analysis of GWAS of generalized anxiety disorder, panic, agoraphobia, social and specific phobias identified common variants associated with an overarching factor (i.e., the Internalizing spectrum), which revealed novel genes (Otowa et al., 2016).

Moreover, the HiTOP model predicts that specific symptom dimensions will have a degree of unique genetic influences, but this assumption remains to be tested. It is plausible that at the lowest level of the hierarchy, unique influences might be largely environmental, in line with the generalist genes hypothesis (Eley, 1997; Plomin & Kovas, 2005). Recent, molecular genetic studies tested this by examining narrow components of disorders (Hodgson et al., 2017). For example, depression subtypes were found to be characterized by partially distinct polygenic liabilities (Milaneschi et al., 2016) and different genetic influences were found for different depression symptoms (Nagel et al., 2017; Thorp et al., 2019). Similarly, a recent GWAS focused on anhedonia among patients with MDD identified 18 variants specific to this symptom dimension, with anhedonia-specific PRS predicting antidepressant treatment efficacy (Ren et

al., 2018). Furthermore, when GWAS targeted another very narrow phenotype - mood instability- four new genetic variants were discovered (Ward et al., 2017). Overall, this provides initial support for the hypothesis of unique genetic effects on lower-order dimensions.

How to HiTOP: a practical guide for genetic studies

There are several practical ways in which psychiatric geneticists can incorporate the HiTOP phenotypic definitions into their research and test HiTOP hypotheses further, as summarized in *Box 1*. Studies in planning stages could consider including measures of dimensional phenotypes that capture transdiagnostic phenotypes, as well as the full dimension of liability to and severity of psychopathology from low to moderate to high, and not just its maladaptive ends captured by case vs. control status (Conway et al., 2010; Greven, Buitelaar, & Salum, 2018; Van Der Sluis et al., 2010). Some of the HiTOP-compatible scales (interview as well as self-report) that allow for higher-order and bifactor modeling are listed in Kotov et al. (2017). Many of these assessments can be administered remotely (e.g. via online surveys accessible on mobile devices) and have been validated in short versions. For example, the Patient Health Questionnaire assesses depression symptoms using nine items (Kroenke, Spitzer, & Williams, 2001). Moreover, abbreviated measures can still capture symptom dimensions, for example the Personality Inventory for DSM-5 consists of 25 items that cover five domains of personality psychopathology (Krueger, Derringer, Markon, Watson, & Skodol, 2013). These measures are suitable for large data collection efforts often required in genetic studies. Furthermore, if diagnostic interviews are used, the studies could aim to assess all symptoms without applying hierarchical exclusion (“skip out”) rules. This may require substantial modifications to interview measures and longer interviewing times, but will allow researchers to

quantify dimensions and assess their hierarchical organization, neither of which is advisable for variables affected by exclusion rules, as these rules usually introduce serious distortions in the data (Kotov, Ruggero, Krueger, Watson, & Zimmerman, 2018). Moreover, skip-out free psychopathology severity dimensions have shown superior validity and reliability over categorical diagnoses derived from the same interview (Shankman et al., 2018).

Another way to capture numerous different traits and the full spectrum of severity is to include measures of personality alongside measures of psychopathology (Krueger et al., 2002; Widiger et al., 2018). Genetic studies of clinical disorders (e.g. alcohol abuse) could assess related traits such as personality pathology (e.g., disinhibition), which are known to precede and contribute to the development of different forms of psychopathology (Hur, Stockbridge, Fox, & Shackman, 2018; Krueger & Tackett, 2006; Shackman et al., 2016; Widiger, 2011) and have been mapped onto the HiTOP model (Widiger et al., 2018). Personality traits may constitute a more stable and thus reliable target for genetic studies than diagnoses, as those are often quite unstable over time (Chmielewski, Clark, Bagby, & Watson, 2015; Markon et al., 2011; Shea et al., 2002), primarily due to unreliability of diagnostic ratings (Regier et al., 2013). In contrast, meta-analyses report that rank-order stability of personality traits reaches .70 in mid to late adulthood (Caspi, Roberts, & Shiner, 2005; Roberts & DelVecchio, 2000). Rank-order stability of normal personality traits is also higher than that reported for psychopathology symptoms (Ormel et al., 2013; Prenoveau et al., 2011).

It is also possible to apply the HiTOP approach when analyzing existing genomic datasets. Many such datasets, for example those collected by the PGC or UK Biobank, are open source or available for secondary analyses upon

request, with detailed instructions on how to access these data posted on Consortia websites. However, such data often contain minimal or categorical phenotyping, with different measures used across studies. We therefore propose a range of approaches for pooling and analyzing these data.

First, pooling of items can be done across different measures and datasets to create higher-order spectra, as long as they are standardized with respect to published population norms, and factor scores can be harmonized by anchoring them to a marker common between datasets. When pooling data, it is recommended to test measurement invariance to ensure that the same construct is captured by different measures or in populations studied across datasets (Vandenberg & Lance, 2000). If invariance is not evident, the data should not be pooled. Second, phenotypes at the desired level of generality within the hierarchy can be derived from both continuous and binary/ordinal variables by employing statistical techniques such as structural equation modelling to derive latent variables, and “bass-ackwards” modelling (Goldberg, 2006).

Third, traditional diagnoses can be scored into dimensional variables at different levels of the hierarchy (e.g. depression severity, internalizing spectrum, general factor) using structural equation modelling, factor analysis or simple counts of diagnoses (Forbes, Tackett, Markon, & Krueger, 2016). If symptom-level data are available, for example because no “skip out” rules were applied in diagnostic interviews or from self-report questionnaires, lower-order quantitative variables can be created, such as using symptom counts or factor analyses to derive empirically coherent syndromes. Often such validated, lower-order components and syndromes can simply be computed by scoring previously-derived subscales within measures. Notably, these techniques flexibly allow for the phenotypes to be derived either within higher-order (variance retained

across levels) or hierarchical (variance divided between levels) frameworks (*Footnote 1*). Finally, this guidance extends beyond analyzing genotypic datasets, as the same principles can be applied to phenotypes included in downstream molecular studies (e.g. methylome and transcriptome data).

Future challenges

A number of outstanding issues remain to be noted. First, shared methods variance could affect the phenotypic structure by inflating loadings on the higher-order factors, or exaggerating associations between symptoms from the same scale. One implication of such potential bias for genetic studies is that GWAS conducted for higher-order latent factors might capture genetic signal that reflects shared methods variance (e.g. constructs related to the response style), alongside the psychopathology. However, bifactor decomposition removes both the variance due to higher-order factors and due to common method biases, leaving specific factors free of both influences. In analyses where shared methods variance is a concern, statistical approaches to remedy measured and unmeasured sources of this confound can be applied to phenotypes prior to conducting genetic analyses (Podsakoff, MacKenzie, Lee, & Podsakoff, 2003). Furthermore, where feasible, future phenotypic and genetic studies could broaden the measurements to include different raters and instruments, something that has been successfully accomplished in very large-scale twin studies (Rimfeld et al., 2019). Notably, genetic structure obtained from twin studies is less affected by this limitation because error is captured by non-shared environmental effects, and common rater effects are usually resolved by relying on correlations across twins' independent reports.

Second, studies that derive structure by analysis of covariation among disorders can be affected by symptom overlap between diagnoses, which also

can affect the genetic structure by inflating the genetic overlap between different scales. This issue can be addressed by analysis of symptom-level data. Third, there are alternative theoretical approaches to interpreting associations among symptoms of psychopathology, most notably network analysis, which posits that covariance of symptoms arise because some symptoms (or their functional consequences) exert causal influences on other symptoms (Borsboom & Cramer, 2013). Consequently, in the network modelling framework, genetic influences are thought to influence individual differences in the strength of the causal relations between the symptoms (i.e. the edges) (Cramer, Kendler, & Borsboom, 2011). Emerging evidence demonstrates that genetic relatedness may indeed moderate associations between individual symptoms (Hasmi et al., 2017; Smeets, Lataster, Viechtbauer, Delespaul, & GROUP, 2014). In the future, generalized network psychometrics that combines network and latent variable models might provide a novel, unified approach to investigating the genetic structure underpinning psychopathology (Epskamp, Rhemtulla, & Borsboom, 2017).

Fourth, although developmental twin and family studies provide support for the alignment of phenotypic and genetic structures within internalizing and disinhibited externalizing spectra, (e.g. Lahey et al. (2011); (Mikolajewski et al., 2013), less is known about other spectra, and age differences and developmental trajectories of the higher-order genetic structure have been explicitly modeled in only a few twin studies (Waszczuk, Waaktaar, Eley, & Torgersen, 2019; Waszczuk et al., 2014; Waszczuk, Zavos, Gregory, & Eley, 2016). A better understanding of genetic influences on psychopathology in young people would inform whether different phenotyping definitions are required when conducting molecular genetic research with developmental samples.

Fifth, while the internalizing, externalizing, and thought disorder spectra, as well as many dimensions within them, have shown cross-cultural generalizability (de Jonge et al., 2018; Ivanova et al., 2007; Ivanova et al., 2015; Krueger, Chentsova-Dutton, Markon, Goldberg, & Ormel, 2003), other parts of the HiTOP model need to be similarly studied. Importantly, structural family and twin studies in non-Western populations are too rare to draw conclusions about the cross-cultural generalizability of higher-order genetic influences on psychopathology. Nonetheless, to date emerging evidence suggests that there may be cross-cultural generalizability (Ball et al., 2011), and genetic influences on normal personality have been shown to be invariant across cultures (Yamagata et al., 2006). Likewise, molecular psychiatric genetic research is limited by its heavy focus on populations of European ancestry (Martin et al., 2018; Torkamani, Wineinger, & Topol, 2018). Until other ancestry-specific GWAS are conducted for a wide range of psychopathology, the cross-cultural generalizability of genetic contributions to mental health cannot be addressed (Docherty et al., 2017).

Sixth, other current limitations of the HiTOP model that may impact its ability to inform genetic research, include no consideration of features such as the age of onset or chronicity, and uncertain placement of developmental disorders, due to paucity of structural data available on this topic (Kotov et al., 2017), and lack of a current validated comprehensive measure of all aspects of the model. Finally, concerning feasibility, expanding phenotypic assessments may increase participant burden and resources needed to conduct the genetic studies, in particular when large sample sizes are required. However, in some cases, such studies may need to add only a small number of psychometrically-sound measures to supplement the existing datasets, and the burden can be reduced by remote data collection, abbreviated instruments, or integration of

information from electronic health records and behavioral tracking via phones or wearable devices. Overall, the extra effort required to obtain comprehensive phenotyping is a worthwhile investment to enable novel research in the field of psychiatric genetics, and a necessary translational step for connecting genotype data to the diverse clinical manifestation of mental illness.

Conclusions

Genetic discovery in psychiatry is hindered by suboptimal phenotypic definitions. We argue that the hierarchical, quantitative, and data-driven classification system proposed by the HiTOP consortium may provide a more effective approach to identifying genetic markers of mental illness than traditional diagnostic categories. The HiTOP approach promises to resolve problems of comorbidity, heterogeneity, and arbitrary diagnostic thresholds that impede progress in psychiatric genetics. In particular, genetic variants are expected to operate at different levels of the HiTOP hierarchy, with some highly pleiotropic genes influencing higher-order psychopathology, and others conferring risk for specific spectra, subfactors, or symptom components. We also demonstrated that the HiTOP model aligns well with our current understanding of the higher-order genetic structure of psychopathology, emerging from biometrical and molecular genetic findings of broad genetic pleiotropy.

Box 1 - How to HiTOP: a practical guide for genetic studies

For studies that are in planning stages:

- Instead of relying exclusively on categorical phenotypes, studies could consider measuring empirically established spectra, and well-defined, validated dimensions within them.
- When diagnostic interviews are included as part of the assessment battery, consider eliminating “skip-out” rules in order to assess a wide range of symptoms even when the person cannot meet diagnostic criteria for given disorder.
- Even studies that aim to focus on a particular disorder would benefit from collecting measures of related forms of psychopathology, including personality, to better capture stable traits underlying disorder risk.

When using existing datasets:

- In instances where phenotypic information is available from diagnostic interviews, it is still often possible to create HiTOP-informed higher-order variables (e.g., internalizing score).
- Likewise, if symptom-level data are available from interview or self-report measures, lower-order quantitative variables can be created.
- When working with both binary/ordinal and continuous data, researchers can employ statistical techniques (e.g. latent variable, “bass-ackwards” modeling (Goldberg, 2006)) to derive phenotypes at a desired level of generality within the hierarchy.
- Higher-order spectra can be created by pooling items across different measures.

- When harmonizing phenotypes from different datasets, quantitative measures can be pooled following standardization with respect to published population norms; factors scores can be harmonized by anchoring them to a marker common between datasets.

Footnote 1

There are two broad, complimentary classes of approaches to modeling the structure of psychopathology: higher-order and hierarchical/bifactor models (Markon, 2019). In higher-order models, general factors explain specific factors, with the latter nested in the former, and general variance is retained as one considers lower levels. The phenotypic HiTOP model is conceptualized as such higher-order model. In hierarchical/bifactor models, general and specific factors are orthogonal and uncorrelated with one another, explaining distinct nonnested components of shared variance among indicators. Higher-order structural biometric models usually consist of hierarchical approach. Thus, when discussing etiological influences, the total genetic variance in psychopathology is often divided into different levels of specificity. Consequently, an intermediate dimension such as the fear subfactor, when conceptualized in the higher-order framework, is influenced by genes operating at different levels of specificity, including general psychopathology genes, genes specific to the internalizing spectrum, and genes specific to the fear subfactor itself. In the hierarchical framework, if the unique phenotypic variance of the fear subfactor is extracted, for example using bifactor modelling (Reise, 2012), it is only influenced by the genes specific to the fear subfactor. The current review operationalizes etiological influences in the hierarchical framework due to this approach being used in biometric studies.

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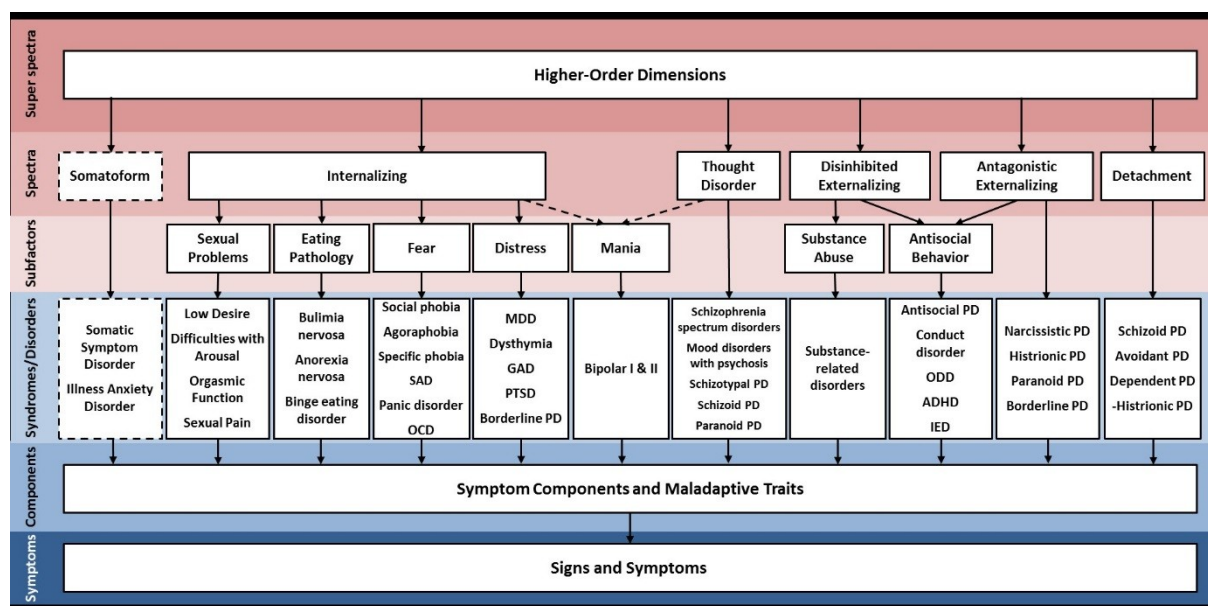
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Figure captions and legends

Figure 1 – The phenotypic HiTOP model.

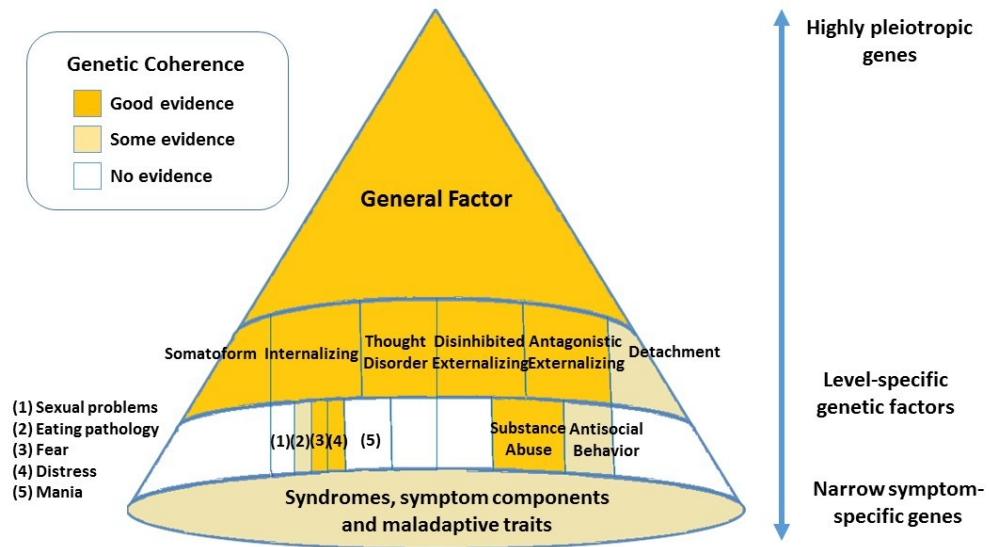


Note: The figure is reprinted from Kotov et al. (2017). Constructs higher in the figure are broader and more general, whereas constructs lower in the figure are narrower and more specific.

SAD – social anxiety disorder, OCD – obsessive-compulsive disorder, MDD – major depressive disorder, GAD – generalized anxiety disorder, PTSD – post-traumatic stress disorder, PD – personality disorder, ODD – oppositional defiant

disorder, ADHA - attention-deficit/hyperactivity disorder, IED - intermittent explosive disorder

Figure 2 - Genetic influences at different levels of the HiTOP hierarchy.



Note:

Genetic variants are expected to operate at different levels of the HiTOP hierarchy, with some highly pleiotropic genes influencing higher-order psychopathology, and others conferring risk for specific spectra, subfactors, or symptom components. For the full literature review supporting genetic coherence at different levels of the HiTOP hierarchy, see *Supplement 1*.