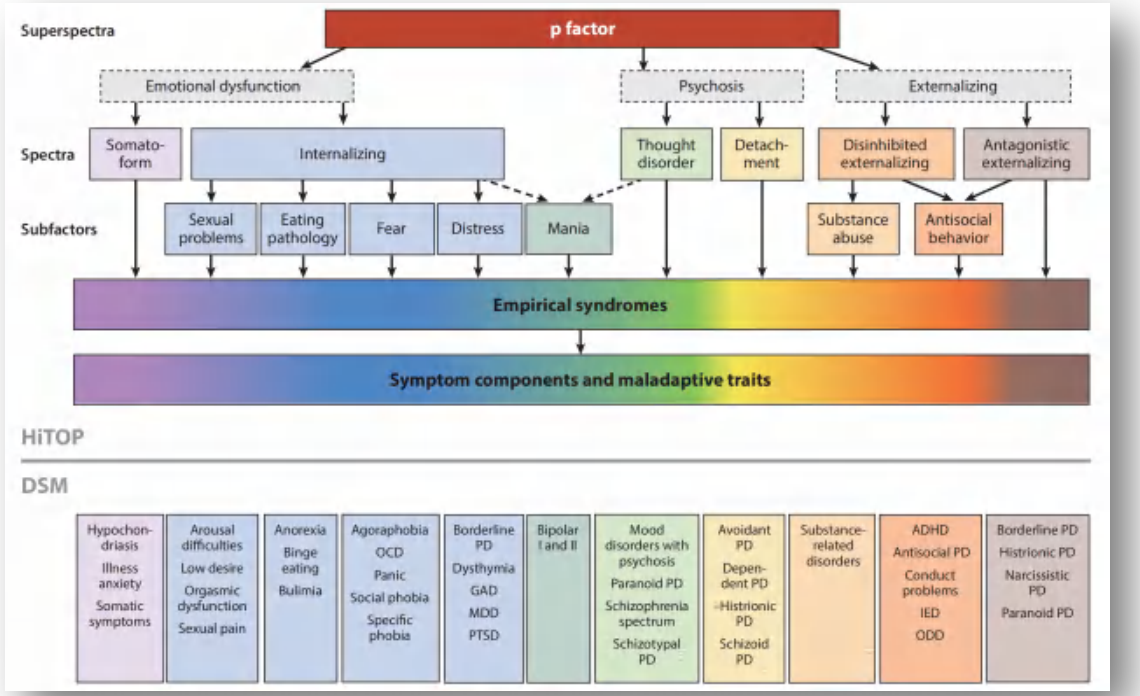

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Developmental Population Neuroscience

发展人口神经科学（精神病理等级分类学）

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State Key Lab of Cognitive Neuroscience & Learning

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Chinese Data-sharing Warehouse for In-vivo Imaging Brain

https://brainder.org/2022/05/04/we-need-better-phenotypes

Article

Reproducible brain-wide association studies require thousands of individuals

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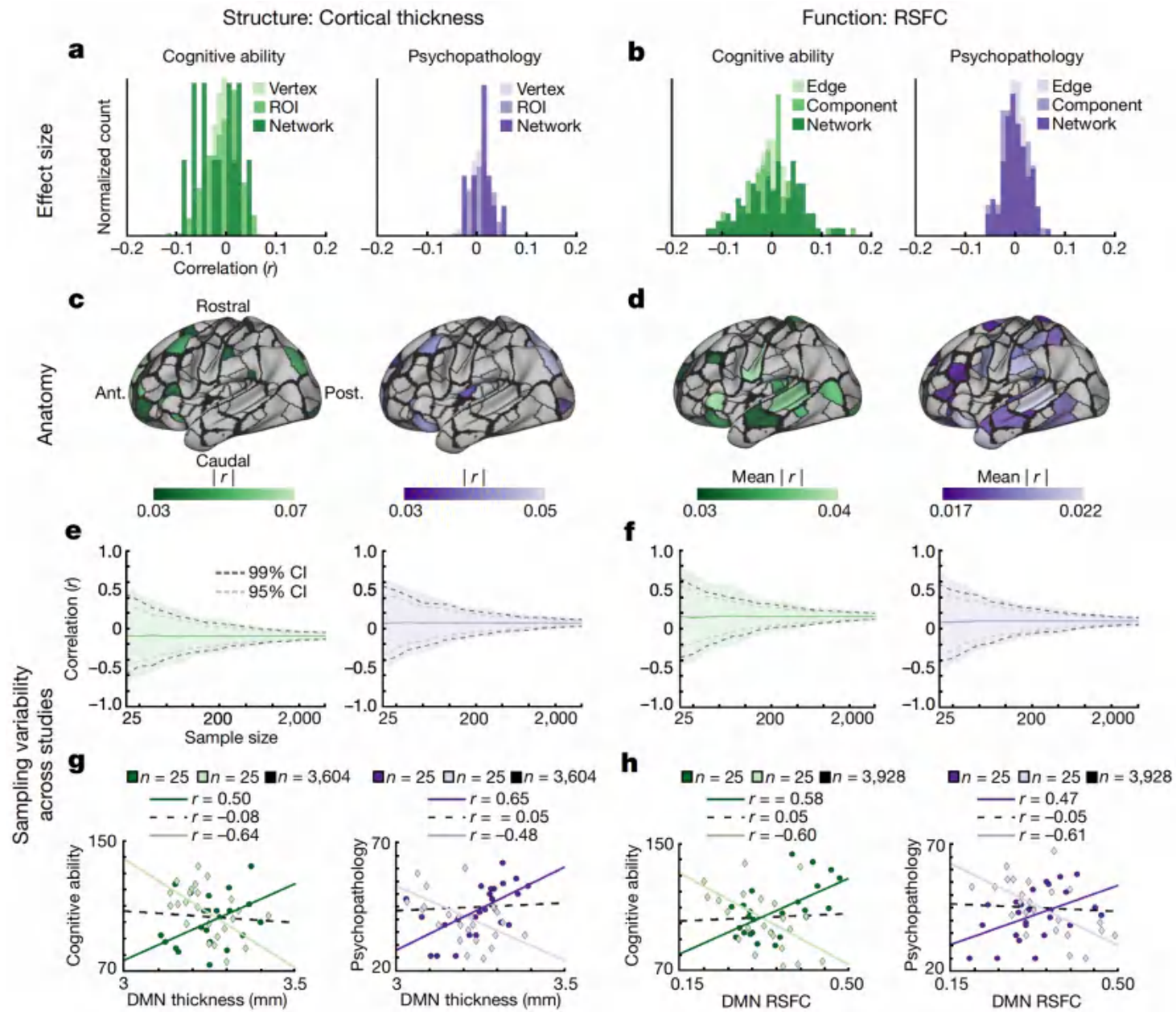
Magnetic resonance imaging (MRI) has transformed our understanding of the human brain through well-replicated mapping of abilities to specific structures (for example, lesion studies) and functions[1–3] (for example, task functional MRI (fMRI)). Mental health research and care have yet to realize similar advances from MRI. A primary challenge has been replicating associations between inter-individual differences in brain structure or function and complex cognitive or mental health phenotypes (brain-wide association studies (BWAS)). Such BWAS have typically relied on sample sizes appropriate for classical brain mapping[4] (the median neuroimaging study sample size is about 25), but potentially too small for capturing reproducible brain–behavioural phenotype associations[5,6]. Here we used three of the largest neuroimaging datasets currently available—with a total sample size of around 50,000 individuals—to quantify BWAS effect sizes and reproducibility as a function of sample size. BWAS associations were smaller than previously thought, resulting in statistically underpowered studies, inflated effect sizes and replication failures at typical sample sizes. As sample sizes grew into the thousands, replication rates began to improve and effect size inflation decreased. More robust BWAS effects were detected for functional MRI (versus structural), cognitive tests (versus mental health questionnaires) and multivariate methods (versus univariate). Smaller than expected brain–phenotype associations and variability across population subsamples can explain widespread BWAS replication failures. In contrast to non-BWAS approaches with larger effects (for example, lesions, interventions and within-person), BWAS reproducibility requires samples with thousands of individuals.

MRI data (such as cortical thickness or resting-state functional connectivity (RSFC)) are increasingly being used for the ambitious task of relating individual differences in brain structure and function to typical variation in complex psychological phenotypes (for example, cognitive ability and psychopathology). To clearly distinguish such BWAS from other neuroimaging research, we formally define them as 'studies of the associations between common inter-individual variability in human brain structure/function and cognition or psychiatric symptomatology'. Classically univariate, BWAS have recently been facilitated by more powerful, but more difficult to interpret multivariate prediction techniques (for example, support vector regression (SVR) and canonical correlation analysis (CCA)). BWAS hold great promise for predicting and reducing psychiatric disease burden and advancing our understanding of the cognitive abilities that underlie humanity's intellectual feats. However, obtaining MRI data remains expensive (approximately US$1,000 per hour), resulting in small-sample BWAS findings that have not been replicated[7–10].

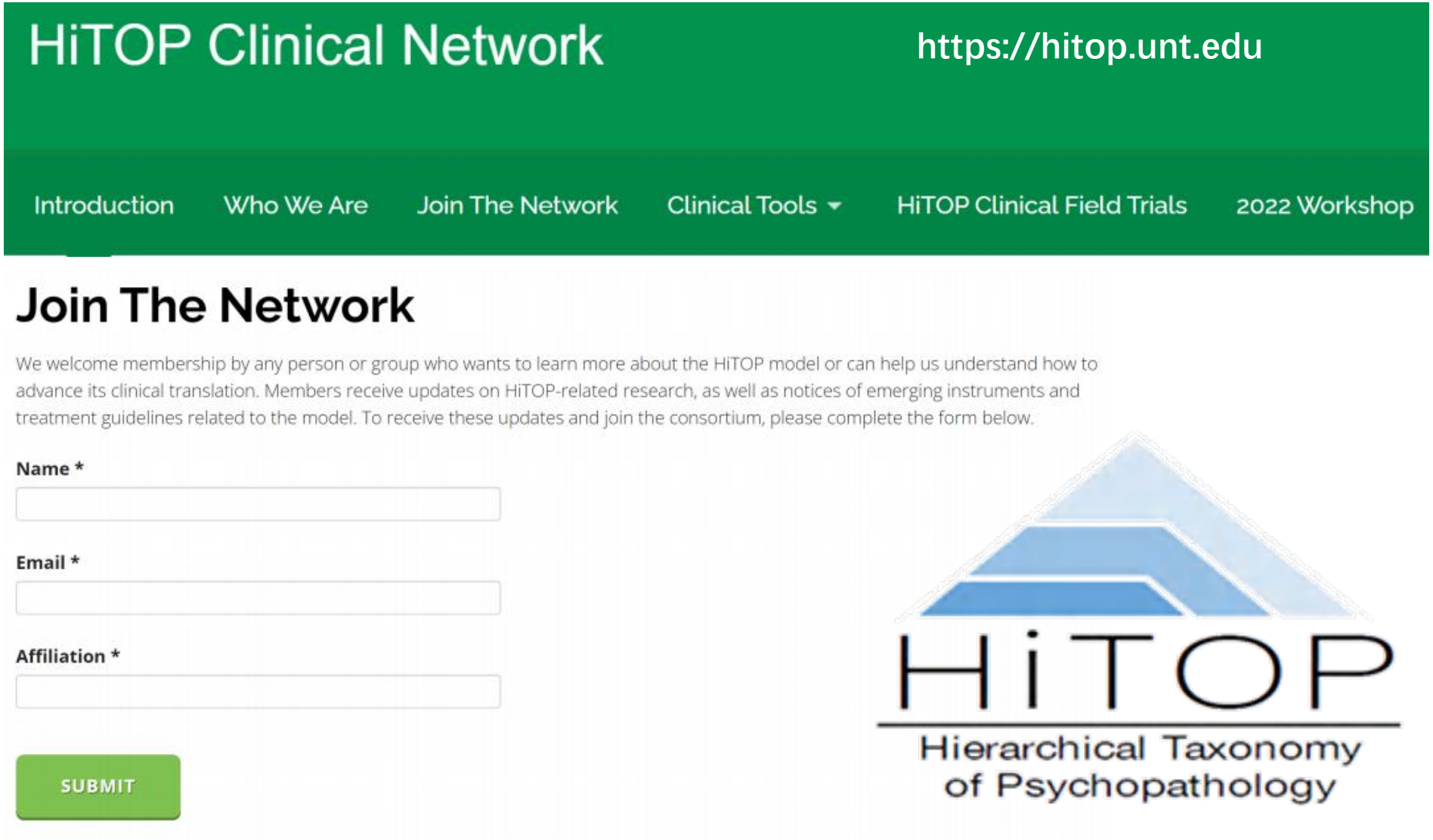
Factors that have contributed to poor reproducibility of population-based research in psychology[11], genomics[12] and medicine[13], such as methodological variability[14], data mining for significant results[15], overfitting[16], confirmation and publication biases[17], and inadequate statistical power[5] probably also affect BWAS. Researchers are starting to address replication failures by standardizing analyses, pre-registering hypotheses, publishing null results and sharing data and code[18]. Nevertheless, there have been concerns that reliance on

A list of affiliations appears at the end of the paper.

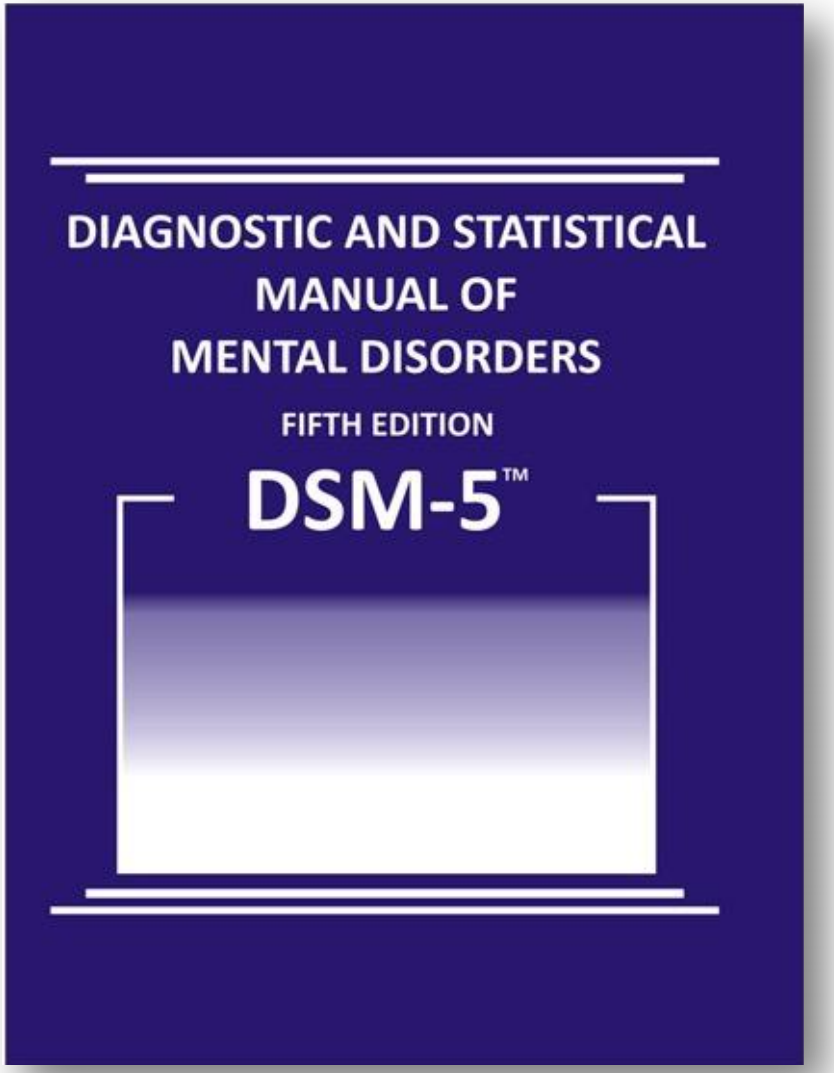


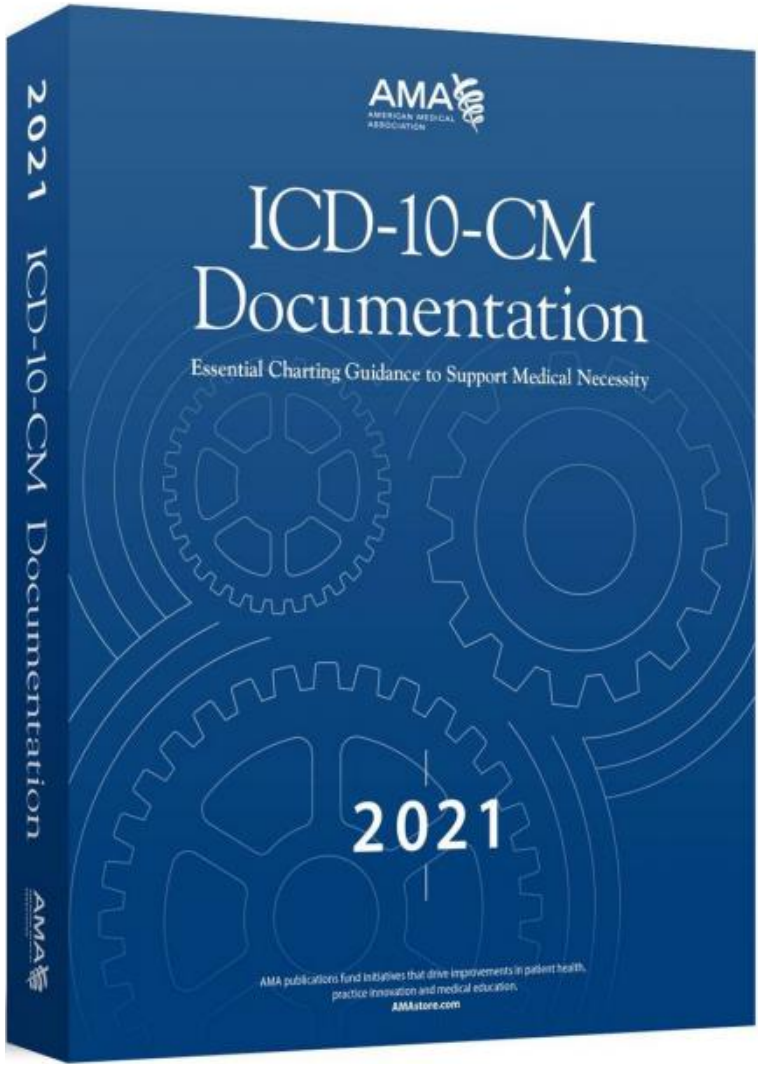
HiTOP (2015) – A Grassroot Effort of Nosologist

HiTOP Clinical Network



Limitations of Traditional Nosologies





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Annual Review of Clinical Psychology

The Hierarchical Taxonomy of Psychopathology (HiTOP): A Quantitative Nosology Based on Consensus of Evidence

Roman Kotov,[1] Robert F. Krueger,[2] David Watson,[3] David C. Cicero,[4] Christopher C. Conway,[5] Colin G. DeYoung,[2] Nicholas R. Eaton,[1] Miriam K. Forbes,[6] Michael N. Hallquist,[7] Robert D. Latzman,[8] Stephanie N. Mullins-Sweatt,[9] Camilo J. Ruggero,[4] Leonard J. Simms,[10] Irwin D. Waldman,[11] Monika A. Waszczuk,[12] and Aidan G.C. Wright[13]

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Limitations of Traditional Nosologies (Experts)

- The fundamental assumption that all mental disorders are **categories** is not supported by data.
- This categorical nomenclature leads to loss of information and reduced **reliability**.
- Traditional systems treat mental disorders as independent conditions, but co-occurrence (i.e., **comorbidity**) among them is very common.
- Many traditional diagnoses are quite **heterogeneous** and include symptoms that have little in common.
- Many patients fall short of the criteria for any DSM-5 diagnosis despite having significant **distress or impairment** that indicates the need for care.

Quantitative Nosology (Nature)

In contrast, quantitative nosology follows findings of structural research to construct the classification of psychopathology (Kotov et al. 2017, Krueger et al. 2018). Rather than relying on the consensus of expert committees, the quantitative approach seeks consensus of studies on the natural organization of mental health. This approach has a history that spans 90 years of research to identify empirical constellations of signs and symptoms (e.g., Achenbach 1966, Eysenck 1944, Krueger et al. 1998, Lorr et al. 1963, Moore 1930, Overall & Gorham 1962, Wittenborn 1951). This work produced influential models and widely used instruments. Similar techniques were used to develop classifications of affect, personality traits, and cognitive abilities (Carroll 1993, Costa & McCrae 2008, Markon et al. 2005, McGrew 2009, Watson & Tellegen 1985). The resulting models achieved wide acceptance in their fields and proved to be effective guides for research and practice.

Importantly, quantitative research not only explicates latent structures but also tests their external validity. Identification of a natural structure is the first step in the development of a nosology, and investigation of its validity is an equally important next step. By 2016, the number of quantitative studies was sufficient for the HiTOP consortium to develop the first version of the system, which was finalized during an in-person meeting at the University of Chicago.

The HiTOP Model: (1) The Principle of Dimensions

Psychopathology is best characterized by **dimensions**, as indicated by extensive research. This approach addresses two shortcomings of traditional diagnoses. Specifically, dimensional description **improves reliability** and **eliminates the need** for Other Specified/Unspecified diagnoses, as every person has a standing on each dimension and thus is described. Nevertheless, some qualitative boundaries may exist in psychopathology. If categorical entities are identified and replicated, they would be added to HiTOP. Indeed, the term dimensional is not used in the name of the model, in recognition of openness to evidence on discrete entities.

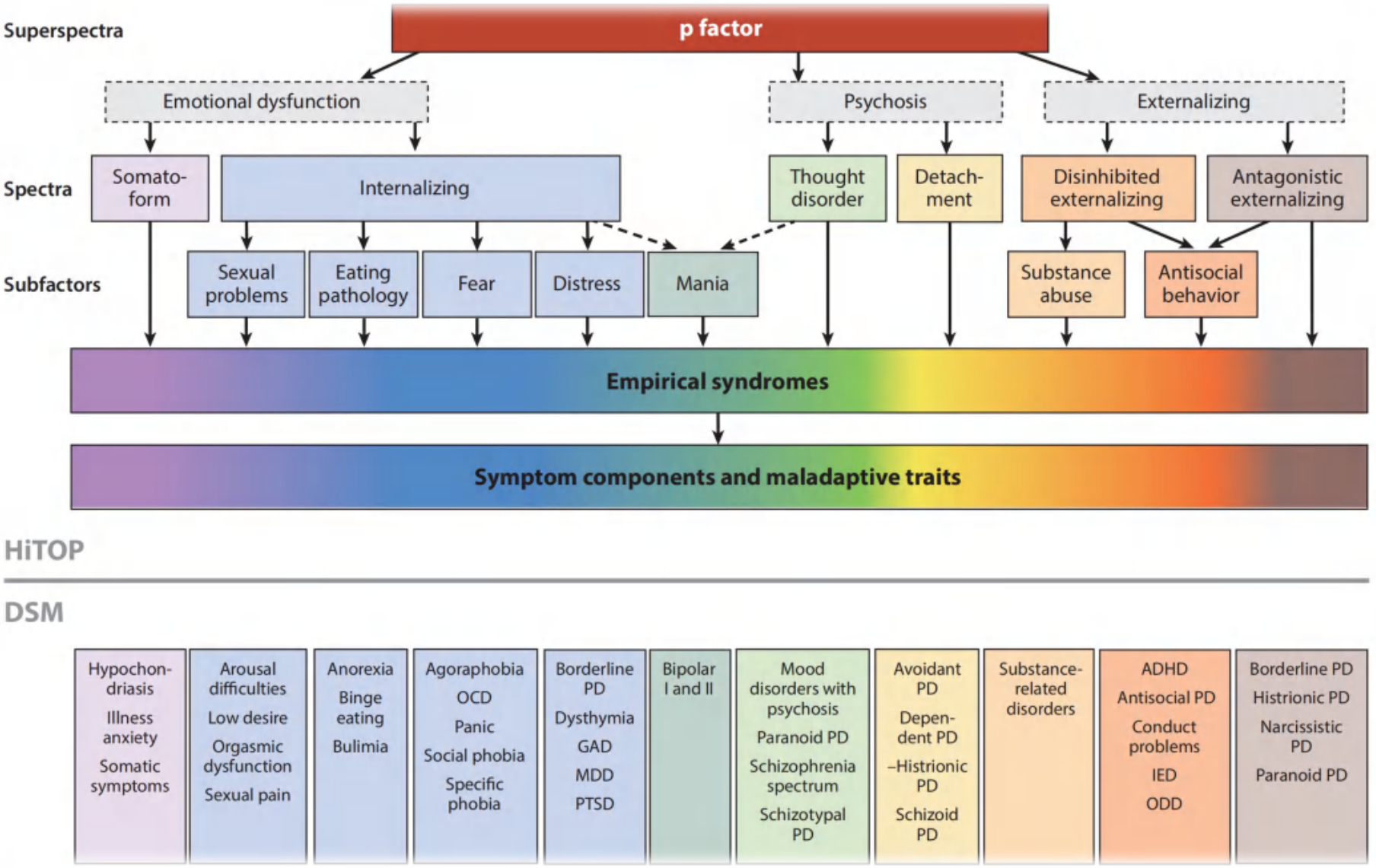
The HiTOP Model: (2) The Principle of Co-occurrence

The natural organization of psychopathology can be discerned in co-occurrence of its features. Classification that follows co-occurrence ensures coherence of diagnostic entities, so that related signs and symptoms are assigned together to tightly knit dimensions, whereas unrelated features are placed on different dimensions. This addresses **the problem of heterogeneity**.

The HiTOP Model: (3) The Principle of Hierarchy

Psychopathology can be organized **hierarchically** from narrow to broad dimensions. Numerous studies have found that specific psychopathology dimensions aggregate into more **general factors**. This hierarchical arrangement addresses the **comorbidity** problem. Patterns of comorbidity are represented by higher-order dimensions. Accordingly, comorbidity is measured and expressed in scores that researchers and clinicians can use. Higher-order dimensions can be targeted to focus on commonalities or alternatively controlled to focus on specific features.

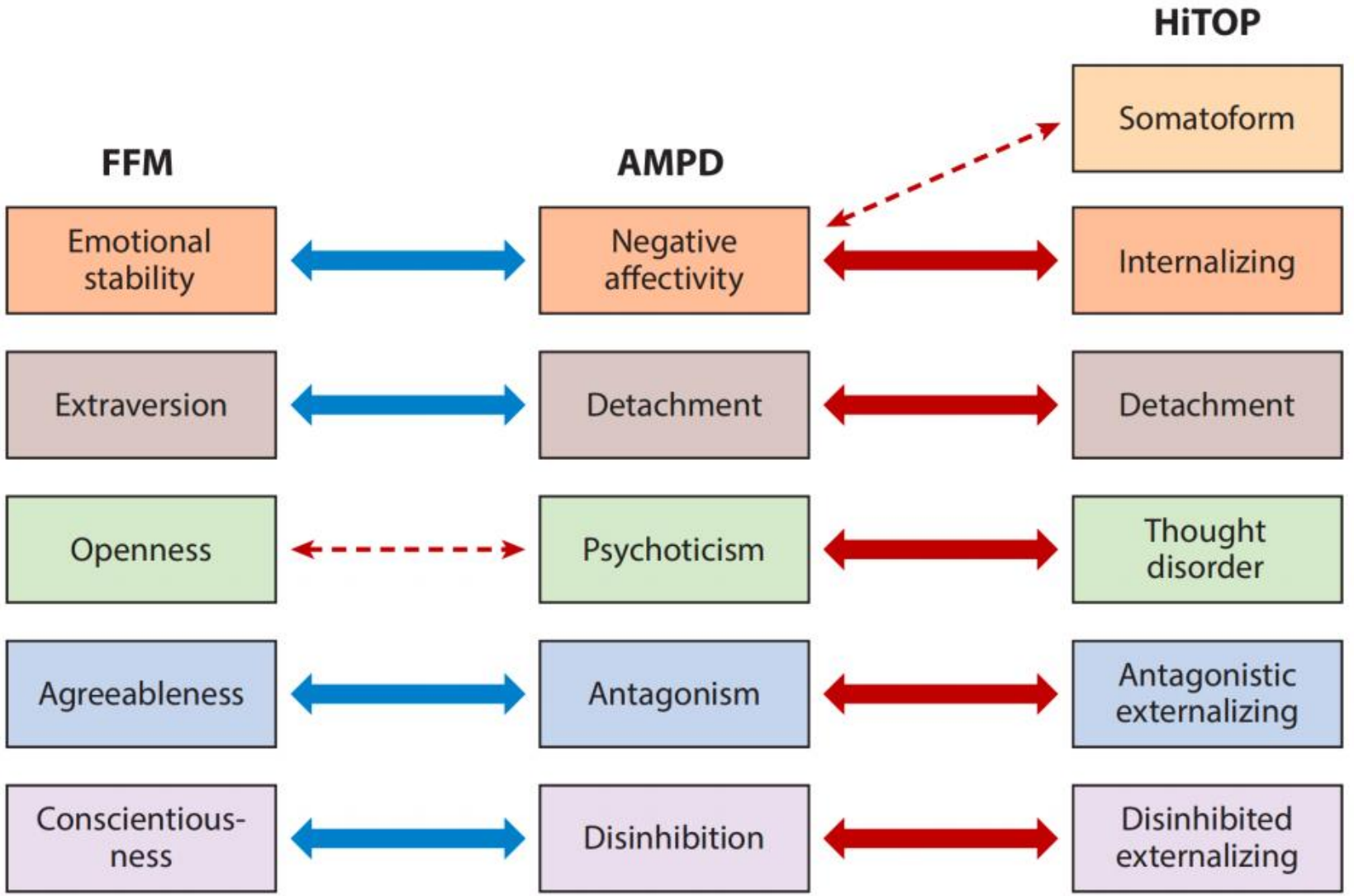
The HiTOP Model



Clinical Ranges

Clinical care often requires categorical decisions, and to be maximally useful, HiTOP needs to specify at what severity level a given action is indicated. Ranges can be identified on dimensions that are each tailored to different clinical actions (e.g., one for initiating antidepressant, another for hospitalization), as has been done in internal medicine for such dimensional variables as blood pressure, cholesterol, and weight (Kraemer et al. 2004). In mental health, this approach was implemented in clinical staging models (Shah et al. 2020). Currently, severity ranges have been specified for HiTOP based on statistical deviance: 1.0–1.5 SD above the mean is mild, 1.5–2.0 SD is moderate, and >2.0 SD is severe (Ruggero et al. 2019b). Such statistical ranges have performed well in other fields, including neuropsychological testing and medical blood tests. However, ranges that are optimized for a specific clinical decision require more complex considerations that weigh rates of false positives and false negatives associated with different cutoffs, costs of the negative outcome, and the effectiveness and cost of the intervention (Stasik-O'Brien et al. 2019). This optimization reflects a balance of costs and benefits, which entails value judgments and is not just a statistical problem. Internal medicine and other disciplines have navigated these challenges successfully and provide good models for HiTOP.

Normal Personality HiTOP Workgroup



Genetic HiTOP Workgroup

Numerous studies have observed genetic factors that align with HiTOP dimensions (Waszczuk et al. 2019). For example, a Swedish national study of >1.5 million siblings identified three genetic factors: general, specific to thought disorder, and specific to nonpsychotic disorders (Pettersson et al. 2016). Nonetheless, genetically informed studies are needed to evaluate the hypothesized genetic structure of several understudied HiTOP dimensions, such as the detachment spectrum and the sexual problems subfactor.

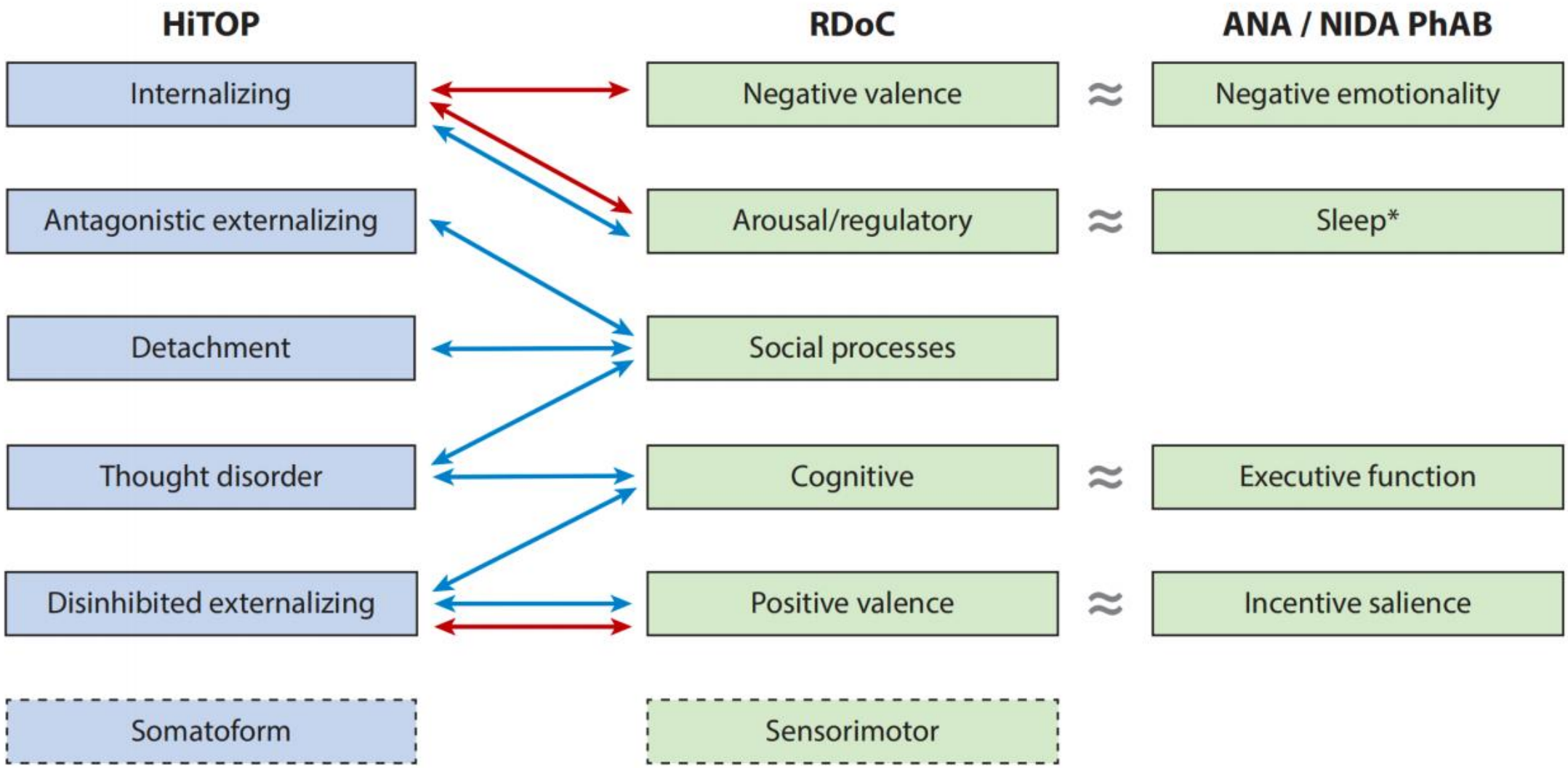
Analyses of genome-wide association studies (GWASs) have been consistent with the behavioral genetic evidence. They have found that a significant proportion of genomic influence is pleiotropic and common to numerous psychiatric disorders, whereas other genetic influences are disorder-specific (Grotzinger et al. 2019, Lee et al. 2019, Selzam et al. 2018). A structure with correlated internalizing, externalizing, thought disorder, and neurodevelopmental spectra has emerged from meta-analyses of GWAS data (Waldman et al. 2020). Overall, existing molecular genetic evidence supports several major HiTOP dimensions, and others can be tested as evidence becomes available for more forms of psychopathology.

Neuroscience HiTOP Workgroup

The Neurobiological Foundations Workgroup investigates links between psychopathology and neurobiological systems as well as the ability of HiTOP dimensions to facilitate clinical neuroscience research. To date, the progress in identifying reliable neurobiological indicators of psychopathology has been limited despite the development of powerful tools for quantifying variation in the human brain. This issue is due primarily to the shortcomings of traditional diagnoses rather than to any inherent limitation of biological approaches to psychopathology (Gordon & Redish 2016, Insel et al. 2010, Latzman et al. 2020). In studies that assessed both diagnoses and dimensions, neural variables were more strongly linked to dimensions (Kircanski et al. 2018, Reininghaus et al. 2019). Diagnoses sometimes showed no associations even when significant results were observed for dimensions.

Numerous studies have confirmed associations between the internalizing spectrum and the extended amygdala as well as the amygdala's connections with the rostral anterior cingulate cortex (Hur et al. 2019, Marusak et al. 2016). A similarly robust literature links the externalizing superspectrum to reduced amplitude of the P300 event-related brain potential, an electrophysiological indicator of reduced cognitive control (Gao & Raine 2009, Venables et al. 2018). Research on the p factor has identified replicable associations with widespread reductions in cortical thickness (Romer et al. 2021). These findings are particularly robust, but many other associations also have been identified between HiTOP constructs and neurobiological markers (Michelini et al. 2020).

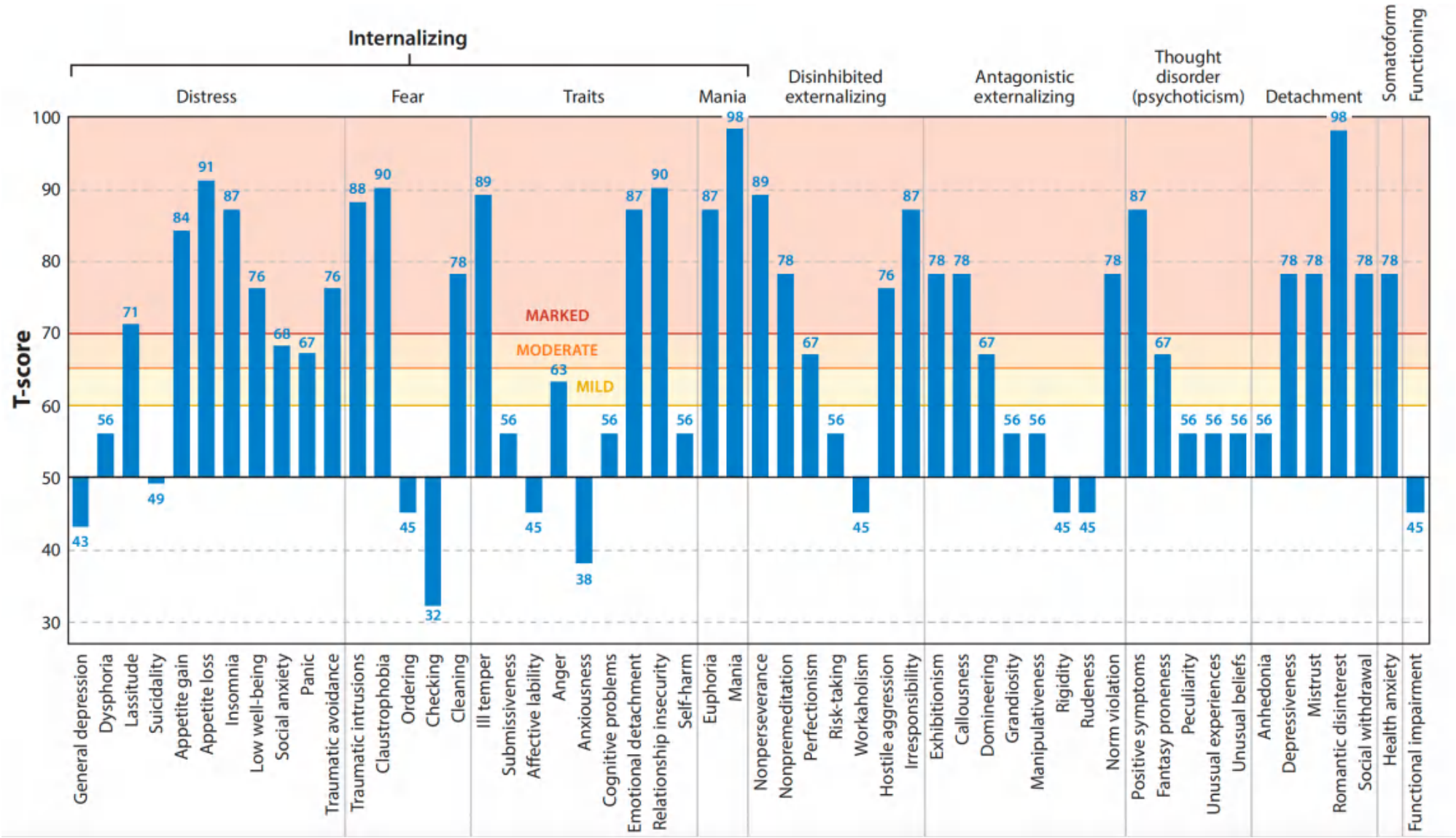
Neuroscience HiTOP Workgroup



Measures Development HiTOP Workgroup

The Measures Development Workgroup includes more than 40 psychometrics experts and is organized in five subgroups structured by spectra (a single externalizing subgroup is responsible for both disinhibited and antagonistic spectra). Construction of measures is proceeding through three phases, guided by the principles of construct-valid scale development (Clark & Watson 2019, Loevinger 1957, Simms & Watson 2007). Phase 1 focused on construct definition and item development, followed by multiple data collections within each spectrum to develop preliminary scales. Scale development principles were articulated collaboratively across subgroups and designed to produce preliminary scales with good internal coherence and discriminant validity within the spectrum. Phase 1 is now complete. Phase 2 will provide cross-validation data. All preliminary scales will be administered together; the goals are to finalize the scales, study their joint structure, collect representative norms, and examine moderators of structure, such as gender/sex and ethnicity/race. Phase 2 will be completed in 2021. Finally, Phase 3 will focus on external validation of the questionnaire scales and development of an accompanying interview to provide another assessment modality. The HiTOP questionnaire will be available for use in 2021, and the interview is ex-

Clinical Translation HiTOP Workgroup



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A Hierarchical Taxonomy of Psychopathology (HiTOP) Primer for Mental Health Researchers

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*All consortium members who contributed to this article are listed in the Transparency section at the end of the article. [1]Department of Psychology, Fordham University; [2]Centre for Emotional Health, Department of Psychology, Macquarie University; and [3]Department of Psychological Sciences, Purdue University

Abstract

Mental health research is at an important crossroads as the field seeks more reliable and valid phenotypes to study. Dimensional approaches to quantifying mental illness operate outside the confines of traditional categorical diagnoses, and they are gaining traction as a way to advance research on the causes and consequences of mental illness. The Hierarchical Taxonomy of Psychopathology (HiTOP) is a leading dimensional research paradigm that synthesizes decades of data on the major dimensions of psychological disorders. In this article, we demonstrate how to use the HiTOP model to formulate and test research questions through a series of tutorials. To boost accessibility, data and annotated code for each tutorial are included at OSF (https://osf.io/8myzw). After presenting the tutorials, we outline how investigators can use these ideas and tools to generate new insights in their own substantive research programs.

Keywords

assessment, classification, Hierarchical Taxonomy of Psychop transdiagnostic, open data, open materials

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Mental health research is at a crossroads. Historically, the field has relied on categorical diagnoses as the basic units of analysis, but there is mounting concern that diagnostic categories, as currently defined, are limiting much needed insights into disorder etiology, treatment, and prevention (e.g., Gordon & Redish, 2016). This criticism has put the focus on *dimensional* perspectives that prioritize phenotypes that cut across traditional diagnostic boundaries (Kotov et al., 2017; Kozak & Cuthbert, 2016).

The Hierarchical Taxonomy of Psychopathology (HiTOP) is an empirically derived model of the major dimensions of mental illness. It represents an alternative research paradigm that, as we argue below, has multiple advantages relative to categorical rubrics. Several publications have described HiTOP's conceptual and empirical foundations (Kotov et al., 2017; Krueger et al., 2018), but as yet, there are no resources that explain

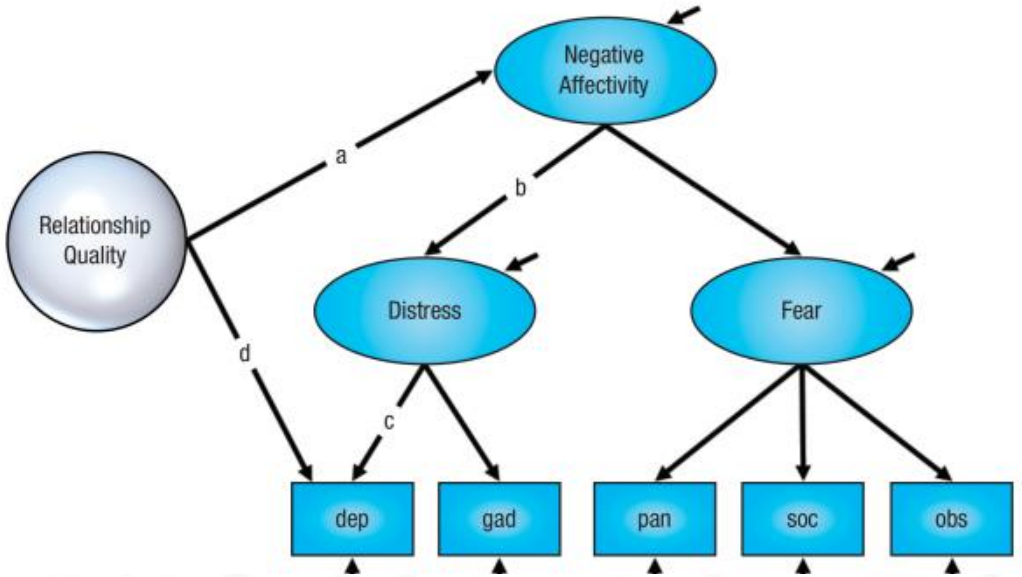


Fig. 2. Direct and indirect effects of relationship quality on emotional-disorder symptoms. This diagram illustrates the regression of the internalizing factor and depression symptoms on relationship quality. The indirect effect of relationship quality on depression via internalizing is represented by the path $a > b > c$. In contrast, the direct effect of relationship quality on depression is represented by path d. These path names mirror the labeling scheme we used in our data analysis code in the Supplemental Material available online. For clarity of presentation, here we omit the indirect pathway from relationship quality to depression via the distress factor. The total effect of relationship quality on depression is the sum of the direct effect (relationship quality > depression), the indirect effect via internalizing (relationship quality > internalizing > distress > depression), and the indirect effect via distress (relationship quality > distress > depression). dep = depression; gad = generalized anxiety; pan = panic; soc = social phobia; obs = obsessions and compulsions. Rectangles represent observed variables, and ellipses represent latent factors. Short, single-headed arrows pointing to distress, fear, and the factor indicators reflect error variances. Single-headed arrows from internalizing to distress and fear represent second-order factor loadings; single-headed arrows from distress and fear to factor indicators are first-order factor loadings.

Highlight HiTOP Strengths

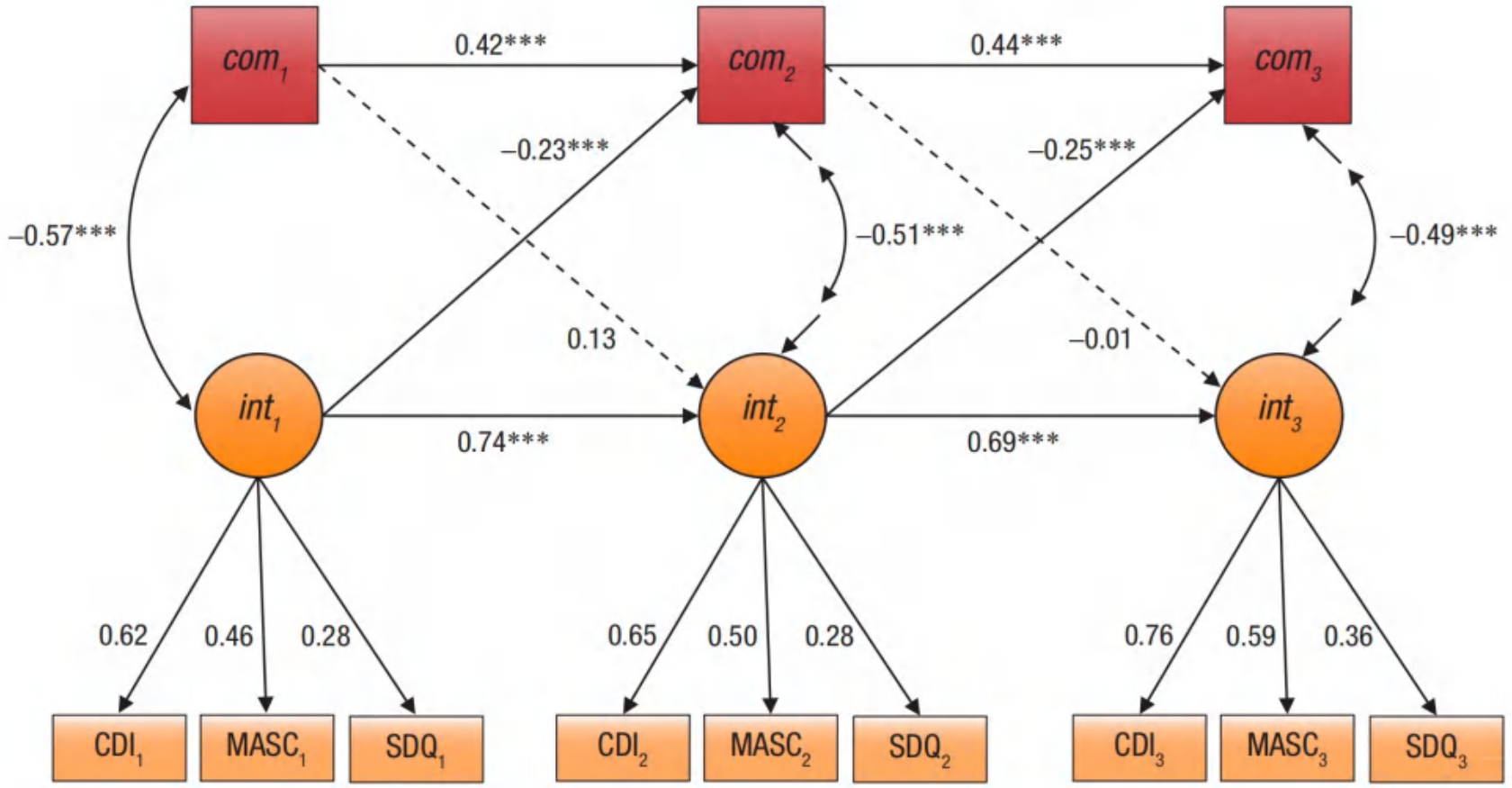
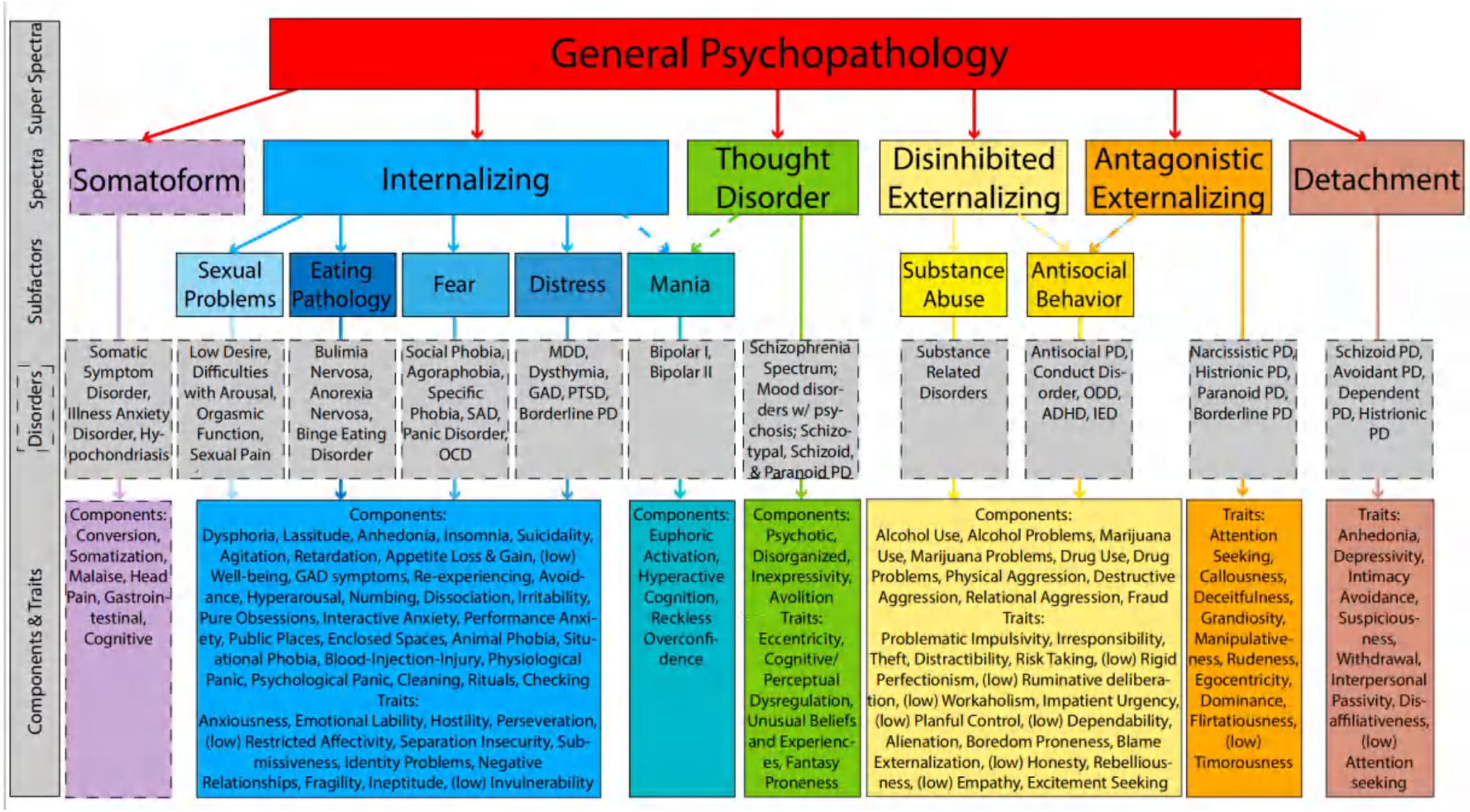
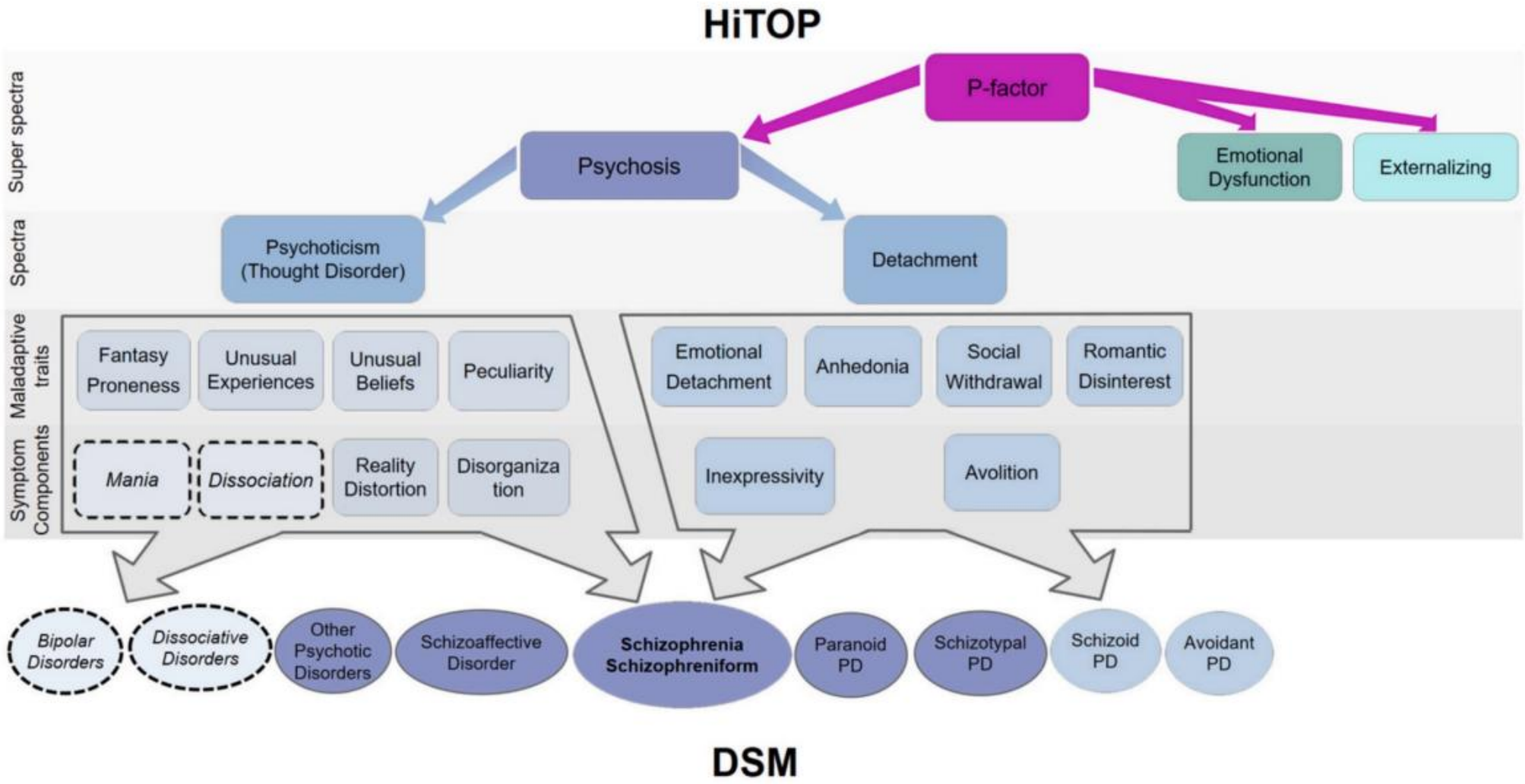


Fig. 3. Cross-lagged panel model of internalizing and social competence over 3 years. All effect sizes are fully standardized (for full results, see Table S6 in the Supplemental Material available). All factor loadings were statistically significant at the .001 α level. Rectangles and circles represent observed and latent variables, respectively. Dashed lines denote statistically nonsignificant paths. *com* = social competence; *int* = internalizing; CDI = Children's Depression Inventory; MASC = Manifest Anxiety Scale for Children; SDQ = Strengths and Difficulties Questionnaire. Asterisks indicate significant paths (***$p < .001$).

Highlight HiTOP Strengths



Highlight HiTOP Strengths



Highlight HiTOP Strengths

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Translating the Hierarchical Taxonomy of Psychopathology (HiTOP) From Potential to Practice: Ten Research Questions

Christopher C. Conway[1], Roman Kotov[2], Robert F. Krueger[3], and Avshalom Caspi[4, 5, 6, 7]

Public Significance Statement

The Hierarchical Taxonomy of Psychopathology (HiTOP) is a rubric for diagnosing mental health conditions. Its basic units are dimensions, on which people differ as a matter of degree, not kind, and these dimensions are arranged in a hierarchy such that psychologists can choose the level of breadth that is appropriate for a given research or clinical task. This article maps the frontiers of HiTOP as it relates to science, practice, and training.

Highlight HiTOP Strengths

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PERSPECTIVE

Using empirically-derived dimensional phenotypes to accelerate clinical neuroscience: the Hierarchical Taxonomy of Psychopathology (HiTOP) framework

Robert D. Latzman, Colin G. DeYoung and The HiTOP Neurobiological Foundations Workgroup

Neuropsychopharmacology (2020) 45:1083–1085; https://doi.org/10.1038/s41386-020-0639-6

Clinical neuroscience seeks to understand the neurobiological mechanisms of mental illness and translate that knowledge into effective, biologically-informed interventions, including pharmacological approaches. The past two decades have witnessed the development of powerful new tools for quantifying variation in the human brain. Nonetheless, although substantial resources and efforts have been invested in identifying reliable neurobiological indicators of mental illness, or "biomarkers", only modest progress has been made. A growing consensus attributes this lack of progress largely to the shortcomings of current categorical diagnostic systems, rather than intrinsic limitations of biological approaches [1].

Categorical diagnoses are suboptimal targets for research on the foundations of psychopathology, and subsequently on the development of biologically-informed interventions, due to their extensive comorbidity, within-disorder heterogeneity, and poor reliability [2]. Within-disorder heterogeneity is so extreme that, for many disorders, two patients may receive the same diagnosis despite sharing few or no overlapping symptoms. Further, no common mental disorder has ever been shown to be categorical rather than dimensional, and the cutoffs used to define diagnoses lack empirical justification, reduce statistical power, and reduce reliability and validity relative to the use of dimensional scores [2].

The U.S. National Institutes of Health (NIH) have responded to this crisis with the NIMH Research Domain Criteria, the NIAAA Addictions Neuroclinical Assessment, and the NIDA Phenotyping Assessments Battery—diagnostically agnostic frameworks formulated by groups of experts around transdiagnostic, biobehavioral systems. Although they place valuable emphasis on neural systems, such frameworks are currently limited in their definition of relevant clinical presentations of mental illness, thus, the relation of these frameworks to patients' suffering, dysfunction in daily life, and potential treatment remains unclear. A complementary framework is needed to link data on biobehavioral systems to the patterns of signs and symptoms that lead people to seek treatment.

An empirically derived, dimensional model of psychopathology can provide just such a framework, working together with the NIH frameworks synergistically to boost their effectiveness. Integrating decades of nosological and psychometric research, the Hierarchical Taxonomy of Psychopathology (HiTOP; https://medicine.stonybrookmedicine.edu/HiTOP) consortium has developed a hierarchical, dimensional model with the potential to encompass the full range of psychopathology (Fig. 1) [2]. At the top levels of the HiTOP hierarchy are broad dimensional spectra and superspectra, including an overarching general psychopathology dimension that reflects broad liability to diverse forms of psychopathology situated lower in the hierarchy. The internalizing spectrum, for example, encompasses more specific subfactors including fear and distress, which, in turn, encompass even narrower clinical phenotypes (e.g., social anxiety, insomnia). Researchers are thus able to test relations with neurobiological mechanisms at multiple levels of the hierarchy in a single study (Fig. 1). Different biological parameters are likely to confer risk at different levels, such that parameters linked to higher levels influence a wider range of related behaviors than those linked to lower levels. This kind of differential pattern has now been observed in a number of MRI studies e.g., refs. [3, 4]. To describe one example, a study of cerebral blood flow in over 1000 youth found that the general factor of psychopathology was associated with elevated perfusion in the anterior cingulate and several other brain regions, whereas subdimensions of fear and psychosis were uniquely related to lower perfusion in the insula and fusiform gyrus, respectively [4].

The HiTOP model provides clinical phenotypes considerably more informative for neuroscience research generally, and for research on potential pharmacological treatments specifically, than current categorical diagnostic systems [2]. HiTOP addresses diagnostic comorbidity by directly modeling which aspects of psychopathology systematically co-occur. It addresses heterogeneity through its hierarchical structure, with broad dimensions at higher levels subdivided into narrower subdimensions at lower levels. Symptoms are organized empirically, such that closely correlated symptoms are assigned to the same dimension and unrelated symptoms to different dimensions. These features, along with the use of dimensions in place of categories, foster increased reliability and precision of measurement. Not surprisingly, therefore, neuroscience research using dimensional constructs consistent with HiTOP is beginning to provide results that appear stronger and more replicable than results from research on categorical diagnoses. For example, meta-analysis identified disruption in fronto-amygdala connectivity as a transdiagnostic neural signature of internalizing psychopathology [5], and a transdiagnostic study of psychotic disorders found that symptom dimensions predict biological differences (twice as well as diagnoses do [6]. Much of this research uses dimensional

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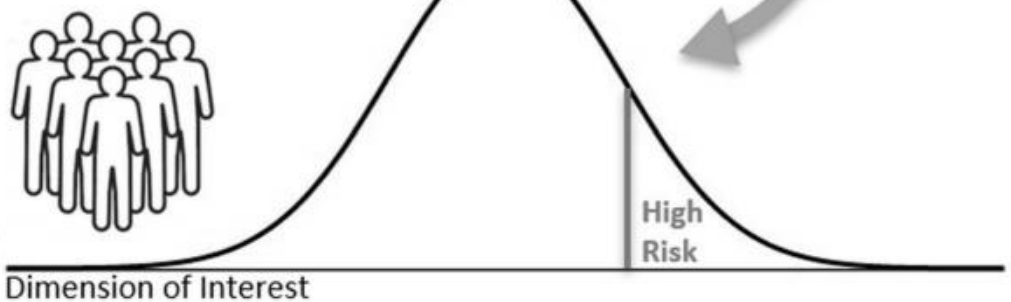
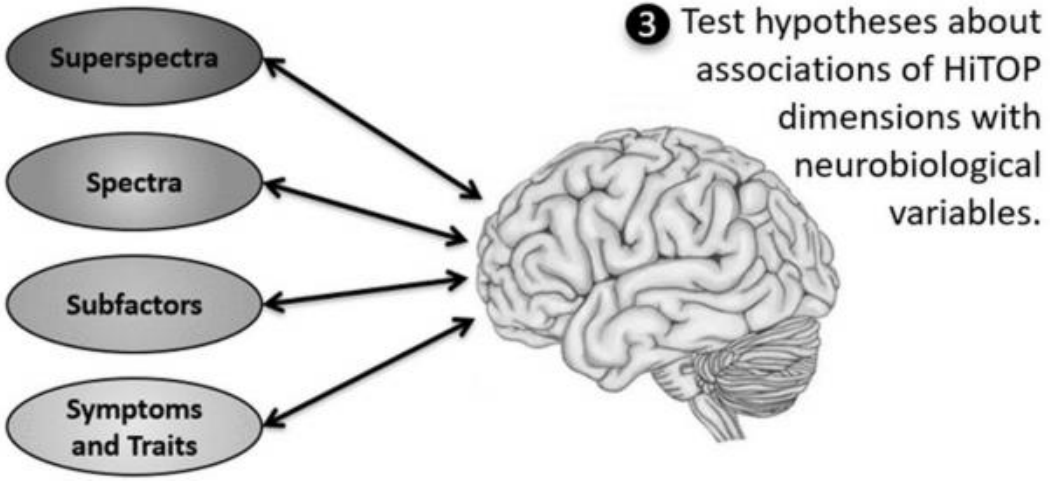
These author contributed equally: Robert D. Latzman, Colin G. DeYoung

HiTOP

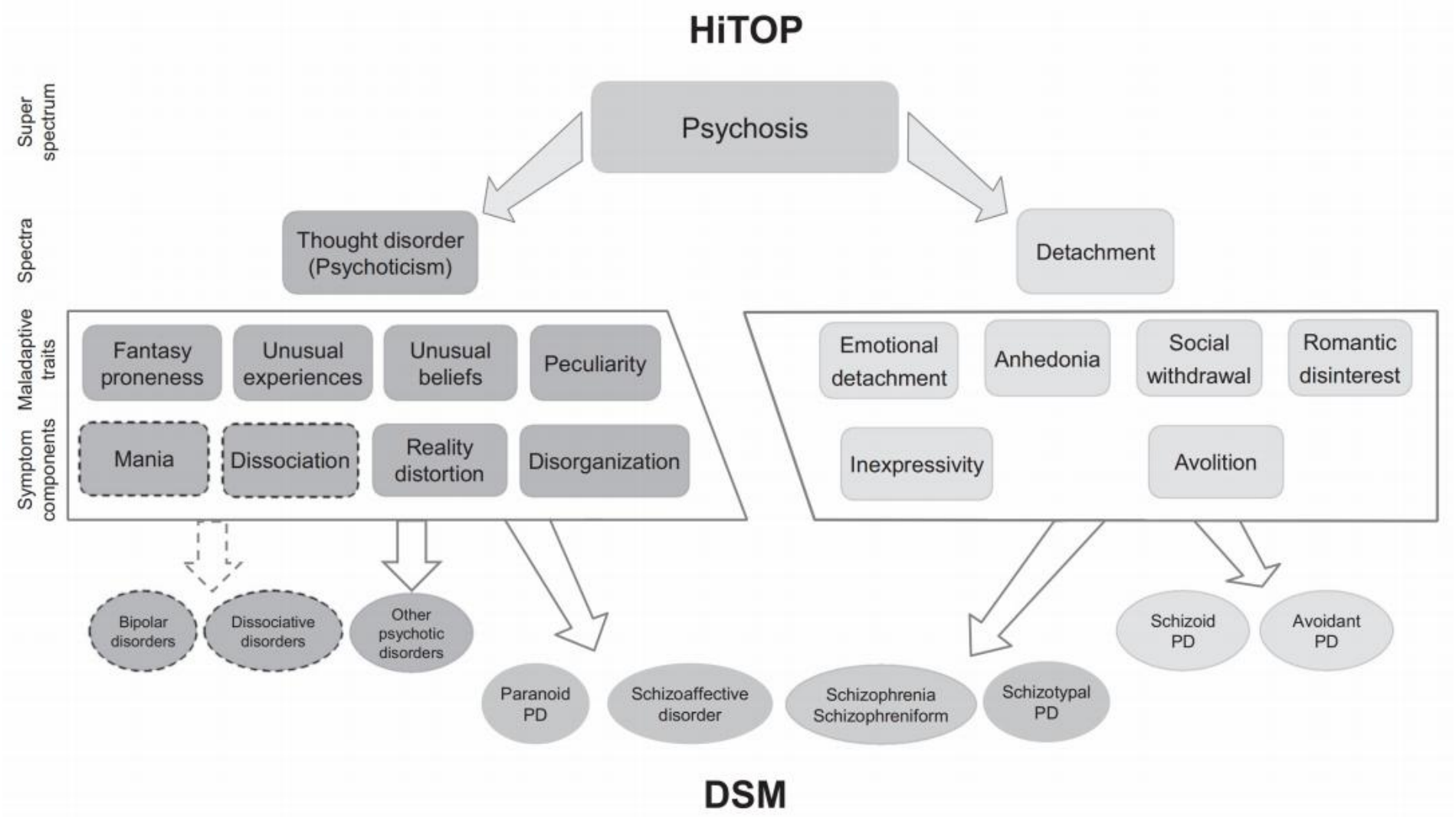
❷ Assess in representative population, potentially oversampling from range of maximal clinical relevance.



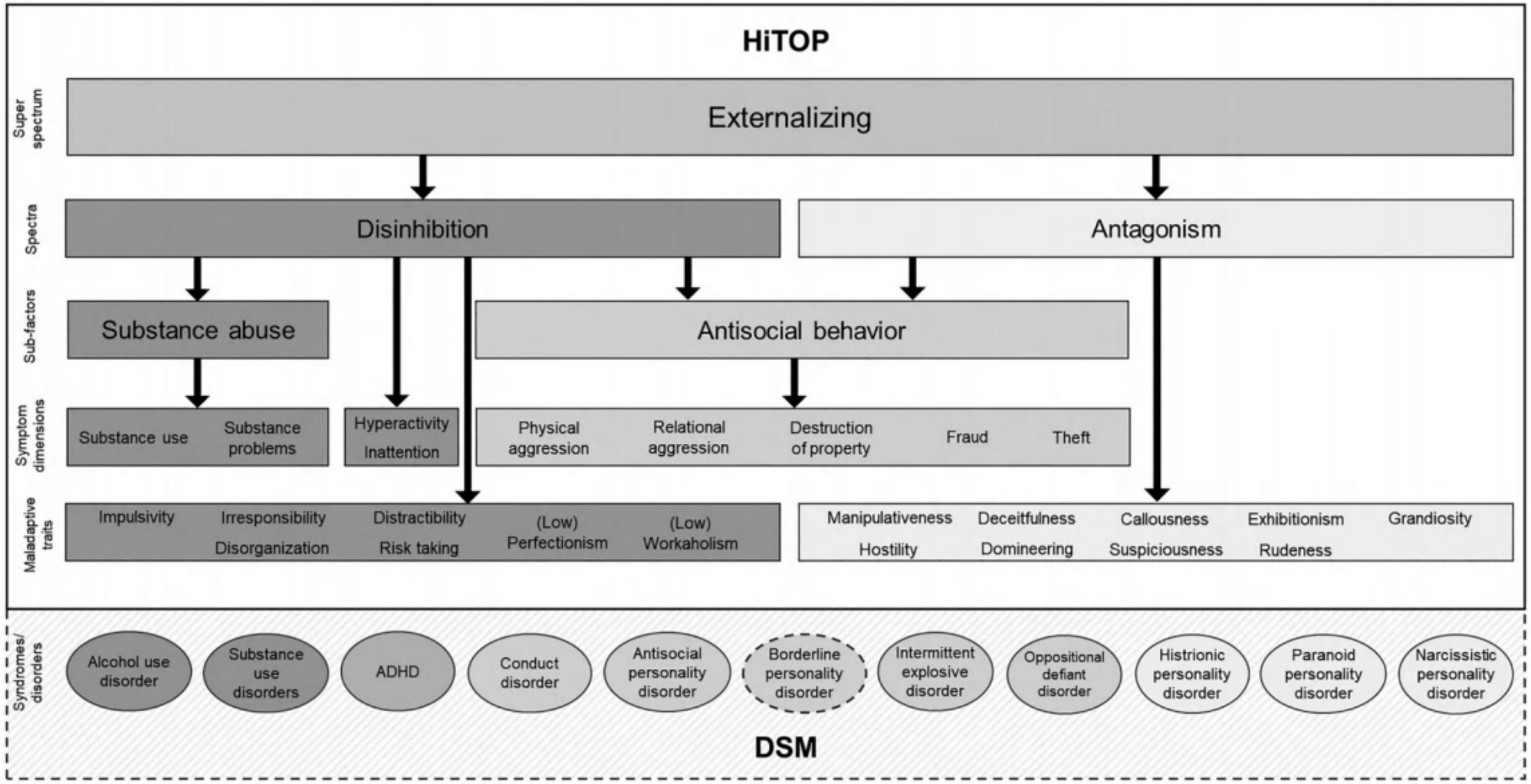
❸ Test hypotheses about associations of HiTOP dimensions with neurobiological variables.



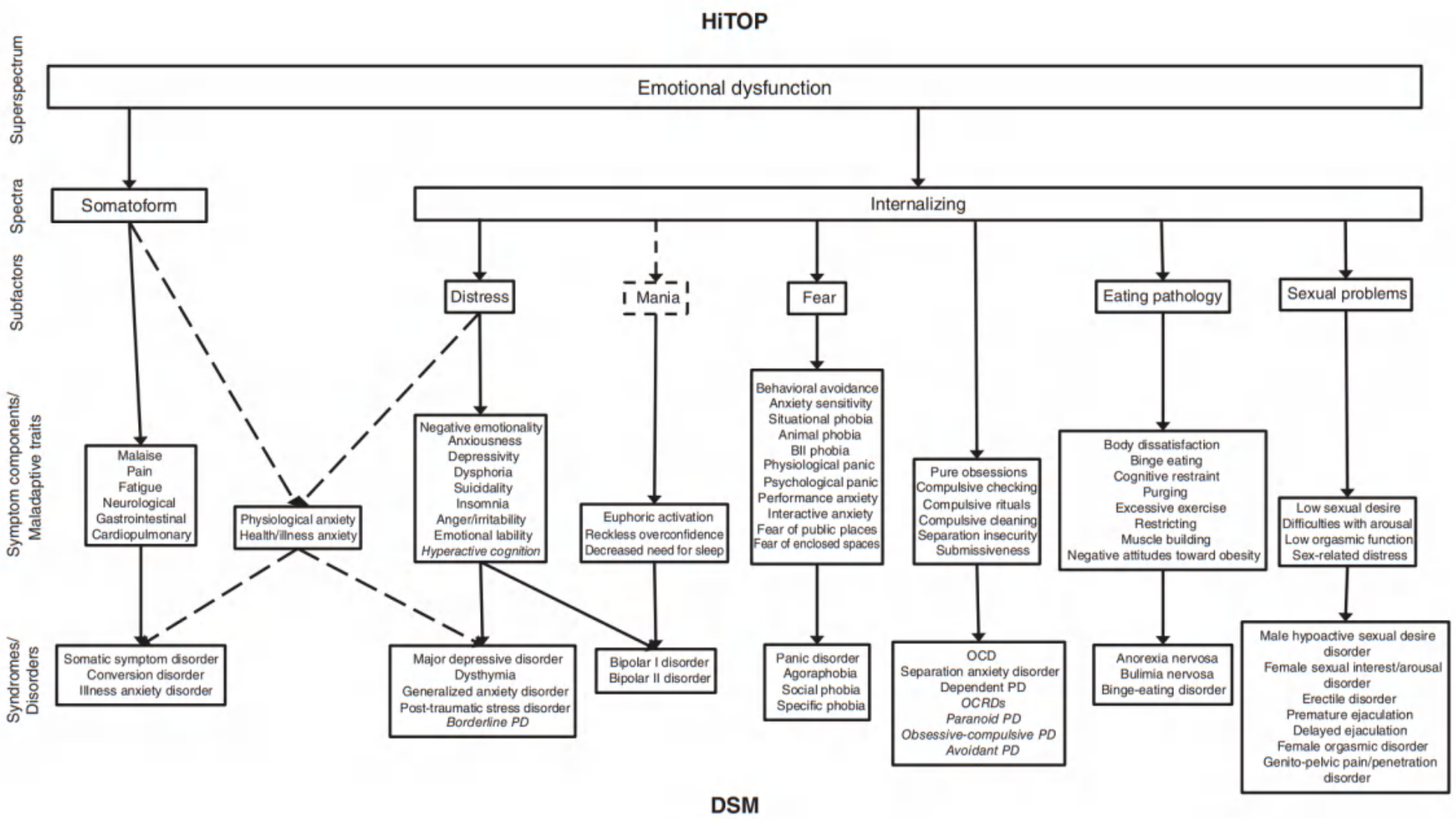
Validity and Utility of HiTOP



Validity and Utility of HiTOP



Validity and Utility of HiTOP



HiTOP Measurements

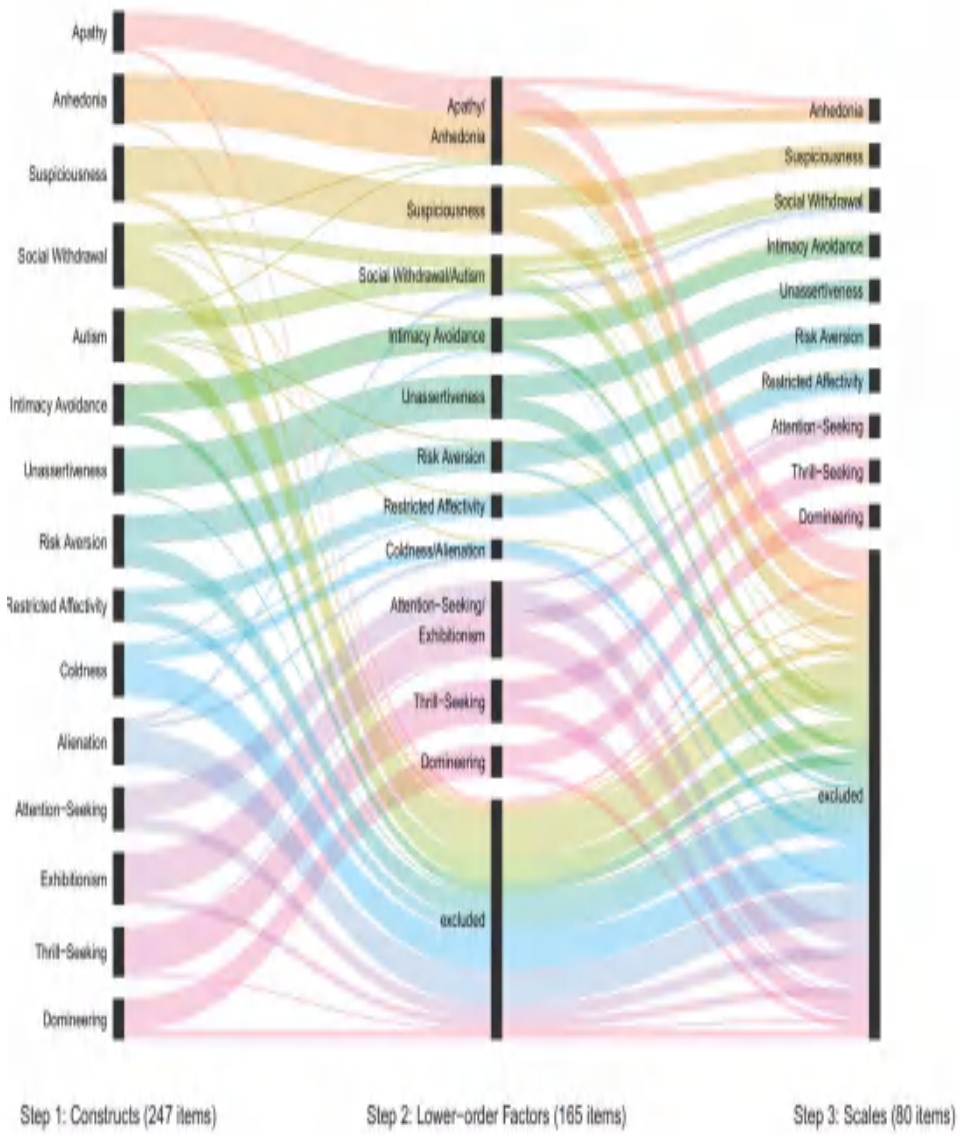
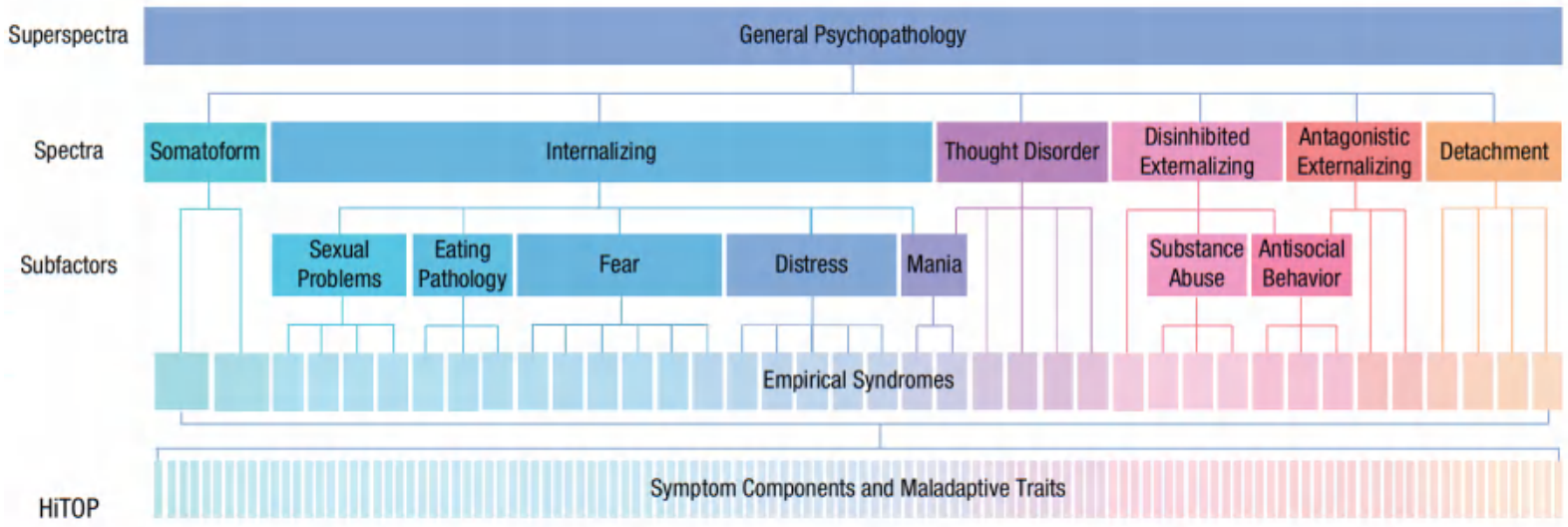
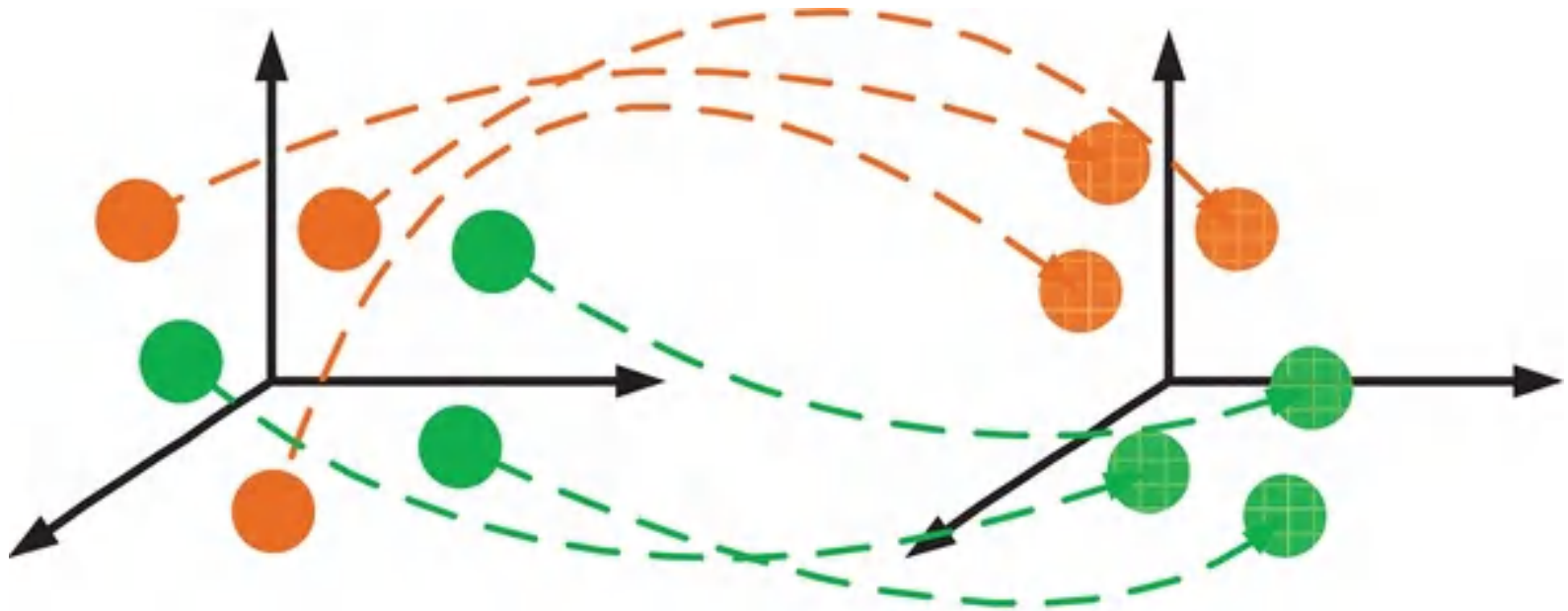


Table 1. Examples of HiTOP-Friendly Measures.

Instrument	Coverage	How to access measure
Achenbach System of Empirically Based Assessment (ASEBA)	Internalizing and disinhibited externalizing spectra	https://store.aseba.org/
Child and Adolescent Psychopathology Scale (CAPS)	Internalizing and disinhibited externalizing spectra	https://www.parinc.com/Products/Pkey/9
Externalizing Spectrum Inventory (ESI)	Disinhibited and antagonistic externalizing spectra	Contact author: cpatrick@psy.fsu.edu
Inventory for Depression and Anxiety Symptoms (IDAS-II)	Internalizing spectrum	Contact author: db.watson@nd.edu
Interview for Mood and Anxiety Symptoms (IMAS)	Internalizing spectrum	https://renaissance.stonybrookmedicine.edu/system/files/IMASInterview.pdf
Scale for the Assessment of Negative Symptoms (SANS)	Thought disorder spectrum	https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/GetPdf.cgi?id=phd000807.2
Scale for the Assessment of Positive Symptoms (SAPS)	Thought disorder spectrum	https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/GetPdf.cgi?id=phd000837.1
Schedule for Nonadaptive and Adaptive Personality–2nd ed. (SNAP-2)	Personality disorder traits	Contact author: lclark6@nd.edu
Personality Inventory for *DSM-5* (PID-5)	Personality disorder traits	https://www.psychiatry.org/File%20Library/Psychiatrists/Practice/DSM/APA. . .
Five Factor Form (FFF)	Personality disorder traits	Contact author: widiger@uky.edu
Five-Factor Model Personality Disorder Scales	Personality disorder traits	Contact author: widiger@uky.edu
Comprehensive Assessment of Traits Relevant to Personality Disorder (CAT-PD)	Personality disorder traits	http://3plab.org/cat-pd/
Dimensional Assessment of Personality Pathology—Basic Questionnaire (BQ)	Personality disorder traits	https://www.sigmaassessmentsystems.com/assessments/dimensional-assessment-of-personality-pathology-basic-questionnaire/
Personality Assessment Inventory (PAI)	Mix of personality traits and psychopathology spectra/ syndromes	https://www.parinc.com/products/pkey/287
Minnesota Multiphasic Personality Inventory–2 Restructured Form (MMPI-2-RF)	Mix of personality traits and psychopathology spectra/ syndromes; covers all six HiTOP spectra	https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Personality-%26-Biopsychosocial/Minnesota-Multiphasic-Personality-Inventory-2-Restructured-Form/p/100000631.html





Original feature space

Joint latent feature space