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A Hierarchical Taxonomy of Psychopathology Can Reform Mental Health Research

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Abstract

For over a century, research on psychopathology has focused on categorical diagnoses. Although this work has produced major discoveries, growing evidence points to the superiority of a dimensional approach to the science of mental illness. Here we outline one such dimensional system—the Hierarchical Taxonomy of Psychopathology (HiTOP)—that is based on empirical patterns of psychological symptom co-occurrence. We highlight key ways in which this framework can advance mental health research, and we provide a heuristic for using HiTOP to test theories of psychopathology. We then review emerging evidence that supports the value of a hierarchical, dimensional model of mental illness across diverse research areas in psychological science. These new data suggest that the HiTOP system has the potential to reform the study of mental health problems and to accelerate efforts to assess, prevent, and treat mental illness effectively.

Keywords: mental disorder, nosology, classification, dimension, transdiagnostic, Hierarchical Taxonomy of Psychopathology (HiTOP), ICD, DSM, RDoC

A Hierarchical Taxonomy of Psychopathology Can Reform Mental Health Research

Dating back to Kraepelin and other early nosologists, research on psychopathology has been framed around mental disorder categories (e.g., *What neural circuit malfunctions characterize generalized anxiety disorder? How does antisocial personality disorder disrupt close relationships?*). This paradigm has produced valuable insights into the nature and origins of psychiatric illness. Yet there is now abundant evidence that categorical approaches to mental illness are hindering scientific progress. Grounded in decades of research, an alternate framework has emerged that characterizes psychopathology using empirically derived dimensions that cut across the boundaries of traditional diagnoses. Recent efforts by a consortium of researchers to review and integrate findings pertaining to this framework have given rise to a proposed consensus dimensional system, the Hierarchical Taxonomy Of Psychopathology (HiTOP; Kotov et al., 2017; see also https://medicine.stonybrookmedicine.edu/HITOP/).

Here, we first summarize the rationale behind dimensional rubrics for mental illness and briefly sketch the topography of the HiTOP system (for detailed reviews, see Kotov et al., 2017, Krueger et al., in press). Second, we explain how HiTOP can be used to improve research practices and theory testing. Third, we review new evidence for the utility of HiTOP dimensions across various research contexts, from developmental psychology to neuroscience. Finally, we offer some practical recommendations for conducting HiTOP-informed research.

A Brief History of HiTOP

Mental illness is a leading burden on public health resources and the global economy (DiLuca & Olesen, 2014; Vos et al., 2016). Recent decades have witnessed the development of improved social science methodologies and powerful new tools for quantifying variation in the genome and brain, leading to initial optimism that psychopathology might be more readily

explained and objectively defined (e.g., Hyman, 2007). Yet, billions of dollars of research have failed to yield new cures, objective assays, or other major breakthroughs (Shackman & Fox, 2018).

A growing number of clinical practitioners and researchers—including the architects of the National Institute of Mental Health Research Domain Criteria (RDoC)—have concluded that this past underperformance reflects problems with categorical diagnoses, rather than any intrinsic limitation of prevailing approaches to understanding risk factors and treatment methods (Redish & Gordon, 2016). Categorical diagnoses—such as those codified in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) and the *International Classification of Diseases* (*ICD*)—pose several well-documented barriers to discovering the nature and origins of psychopathology, including pervasive comorbidity, low symptom specificity, marked diagnostic heterogeneity, and poor reliability (Clark, Cuthbert, Lewis-Fernández, Narrow, & Reed, 2017; Helzer et al., 2009; Markon, Chmielewski, & Miller, 2011; Regier et al., 2013). Regarding reliability, for instance, *DSM-5* field trials found that approximately 40% of diagnoses examined did not reach the cutoff for acceptable inter-rater consistency (Regier et al., 2013). Attesting to symptom profile heterogeneity in *DSM*, there are over 600,000 symptom presentations that satisfy diagnostic criteria for *DSM-5* posttraumatic stress disorder (Galatzer-Levy & Bryant, 2013).

Addressing these problems requires a fundamentally different approach. HiTOP—like other dimensional proposals, such as RDoC (e.g., Brown & Barlow, 2009; Cuthbert & Insel, 2013)—focuses on continuously distributed traits theorized to form the scaffolding for psychopathology. In the tradition of early factor analyses of disorder signs and symptoms in adults (e.g., Eysenck, 1944; Moore, 1930) and children (e.g., Achenbach, 1966), more recent quantitative analysis of psychological symptom co-occurrence has established a reproducible set of dimensions theorized to reflect the natural structure of psychological problems (Kotov et al., 2017).

Figure 1 provides a simplified schematic depiction of HiTOP, which features broad, heterogeneous constructs near the top of the model and specific, homogeneous dimensions near the bottom. HiTOP accounts for diagnostic comorbidity by positing dimensions (e.g., internalizing) that span multiple *DSM* diagnostic categories, and it also models diagnostic heterogeneity by specifying fine-grain processes (e.g., worry, panic) that constitute the building blocks of mental illness.

HiTOP is a work in progress. An international group of researchers has assembled to investigate this structure and update it as informed by new data (Krueger et al., in press). (The HiTOP consortium will publish revisions to Figure 1, as new research findings come in, on the Open Science Framework: https://osf.io/3kq9g/.) Refining this dimensional model is a key priority, but it is only the first step in the evolution of HiTOP. The next phase is to use HiTOP to improve and accelerate research focused on mental health and illness. As described in more detail below, HiTOP has the potential to advance theories of psychopathology and make mental health research more efficient and informative.

HiTOP as a Psychopathology Research Framework

A distinguishing feature of HiTOP is its *hierarchical layout* (Figure 1). Various processes—some specific, others quite broad—are potentially implicated in the origins and consequences of psychological problems across the lifespan (Forbes, Tackett, Markon, & Krueger, 2016). The hierarchical structure implies that any cause or outcome of mental illness could emerge because of its effects on broad higher order dimensions, the syndromes, or specific lower order dimensions (Figure 2). Take trauma, for example. Suppose that research based on the HiTOP model establishes that trauma exposure better predicts variation in the internalizing spectrum than in its constituent syndromes (e.g., depression, posttraumatic distress). How would this result change our conceptualization of this research area? It would call for an expansion of our

etiological models of posttraumatic distress to focus on the broad internalizing spectrum, including psychobiological processes shared by the mood and anxiety disorders. We might advise a moratorium on research studies that examine only one *DSM* disorder in relation to trauma exposure; instead, for maximum efficiency, we would consider various aspects of the internalizing spectrum (e.g., worry, rituals, insomnia, irritability) as outcomes *simultaneously* in research studies. Additionally, when making policy decisions regarding prevention and intervention resources, we might prioritize screening trauma-exposed individuals for the full range of internalizing problems, not just PTSD. In sum, thinking hierarchically about mental illness can promote more efficient research practices and more nuanced theory.

To illustrate these points, we now consider a more detailed example of putting HiTOP into practice (Figure 3). Here, for ease of presentation, *DSM* diagnoses comprise the basic units of assessment. We emphasize, however, that it is optimal from a HiTOP perspective to orient data collection around more homogeneous signs and symptoms of mental disorder (e.g., Markon, 2010; Waszczuk, Kotov, Ruggero, Gamez, & Watson, 2017). A subset of HiTOP constructs are involved: in decreasing order of granularity: the internalizing spectrum; fear, distress, and eating pathology subfactors; and their component syndromes (e.g., binge eating disorder, agoraphobia). These constructs serve as the predictor variables here.

For this example, we consider a test of an autonomic stress reactivity theory of social phobia. The outcome of interest is skin conductance level during an impromptu speech delivered to a group of impassive confederates. The researchers' theory—which, like many others in psychopathology research, pertains to *one* particular categorical disorder—dictates that predictive path *a* in Figure 3 should eclipse the others: the social phobia diagnosis should be specifically associated with exaggerated autonomic reactivity in this evaluative social context. Alternatively, one could reasonably expect that excessive autonomic reactivity is a more general characteristic of

fear disorders (e.g., social phobia, panic disorder, agoraphobia), as compared to distress or eating pathology syndromes. In that case, path *b* should surpass the others in terms of variance explained. Finally, given evidence linking the full complement of anxiety and depressive disorders to stress responsivity, it is possible that reactivity is best captured at the spectrum level. In this last scenario, path *c* should predominate.

This heuristic illustrates that examining the validity of any *DSM* diagnosis in isolation—a conventional research strategy—is unnecessarily limiting. A zero-order association between a *DSM* diagnosis and some outcome could reflect one (or more) qualitatively distinct pathways (in our example, paths *a*, *b*, or *c* in Figure 3). Hierarchical models, like HiTOP, provide a ready means of quantitatively comparing these alternatives. If, in our example, the effect for path *a* is comparatively small, the research team will know to revise the "autonomic arousal theory of social phobia" to encompass fear-based or internalizing disorders more generally.

We supplement this case study with a real-world example of theory building driven by HiTOP. The *stress generation* theory posits that individuals with *DSM* major depression encounter more stressful life events—including ones they have had a role in creating (e.g., romantic relationship dissolution, school expulsion)—than non-depressed counterparts (Hammen, 1991). Indeed, there is evidence that depression prospectively predicts stress exposure. But more recent work suggests that this effect is not specific to depression. In fact, stress generation appears to be a general feature of the internalizing disorders and dispositional negativity (Liu & Alloy, 2010). Consistent with this hypothesis, Conway and colleagues demonstrated that the internalizing spectrum, externalizing spectrum, and *DSM* major depression all contributed to the prediction of future stress exposure when considered simultaneously (cf. Figure 3; Conway, Hammen, & Brennan, 2012). Interestingly, panic disorder had an *inverse* effect on stress occurrence after

adjusting for the transdiagnostic dimensions. The authors labeled this novel association a “stress inhibition” effect.

These findings prompted a reformulation of stress generation theory. First, stress generation processes are now hypothesized to operate across a range of internalizing and externalizing syndromes, not just *DSM* major depression. Second, the HiTOP-consistent analysis pointed to a role for depression-specific pathology in predicting stressful events above and beyond the effects of the internalizing spectrum (i.e., incremental validity). Theorists can use that result to consider the specific portions of *DSM* major depression that increase the likelihood of encountering significant stressors. Third, this work highlights the need to understand more fully the stress inhibiting consequences of panic symptoms, a signal that was not detectable when analyzing *DSM* diagnoses only.

Up to this point, we have considered how a hierarchical approach—that is, comparing pathways to and from dimensions across higher and lower levels of the HiTOP structure—can advance our understanding of psychopathology. Although this research strategy has been the most common application of HiTOP, it is hardly the only one. Some researchers have used HiTOP to dissect *DSM* diagnoses into components and assess their relative criterion validity (e.g., Simms, Grös, Watson, & O’Hara, 2008) (Figure 2b). For example, panic disorder could be decomposed into physiological (e.g., tachycardia, choking sensations) and psychological symptoms (e.g., thoughts of dying or going crazy). The predictive validity of these two symptom domains could then be compared in relation to a clinical outcome of interest (e.g., emergency room visits). Other researchers have evaluated the joint predictive power of sets of HiTOP dimensions above and beyond the corresponding *DSM-5* diagnosis (see Waszczuk, Kotov, et al., 2017; Waszczuk, Zimmerman, et al., 2017). This approach explicitly compares the explanatory potential of dimensional versus categorical approaches to psychopathology (Figure 2c).

Investigators are beginning to use these research strategies to reevaluate existing theories and findings through a HiTOP lens. In the sections that follow, we describe studies that have approached etiological and clinical outcome research from a HiTOP perspective as a way of selectively illustrating its utility.

Etiological Research from a HiTOP Perspective

Quantitative and Molecular Genetics. Genetic studies show that some HiTOP dimensions—which were empirically derived from covariance among outward phenotypes—can be connected to distinct genetic liability factors. That is, the phenotypic and genetic structures of psychopathology are largely aligned (e.g., Lahey, Krueger, Rathouz, Waldman, & Zald, 2017; Røysamb et al., 2011). Twin studies show that anxiety and depressive disorders have a common genetic diathesis, whereas antisocial behavior and substance use conditions share their own genetic factor (Kendler & Myers, 2014). Further, twin research shows that psychiatric syndromes—and even certain symptom components within them—possess, at least to an extent, unique genetic underpinnings in addition to genetic risk shared with related disorders (e.g., Kendler, Aggen, & Neale, 2013; Rosenström et al., 2017). Although these specific genetic factors often are comparatively small, they support a hierarchical conceptualization of psychopathology *at the etiological level*.

Further attesting to the hierarchical structure of genetic risk, twin research has documented an overarching genetic liability factor that resembles a general factor of psychopathology (Pettersson, Larsson, & Lichtenstein, 2016). This general factor (see top level of Figure 1) was first described in phenotypic analyses (Lahey et al., 2012) and was termed the "*p*-factor" as a counterpart to the *g*-factor in the intelligence literature (Caspi et al., 2014). Consistent with the broad intercorrelations among higher order spectra in psychometric studies, there is growing evidence that common genetic vulnerabilities underlie a general (i.e., transdiagnostic) risk for

psychopathology. At a lower level of the hierarchy, distinct genetic influences have been identified for the distress and fear subfactors of the internalizing spectrum (Waszczuk, Zavos, Gregory, & Eley, 2014). Also, there is a consistent, but underdeveloped, line of twin research that provides biometric support for the genetic coherence of the thought disorder (Tarbox & Pogue-Geile, 2011) and detachment (Livesley, Jang, & Vernon, 1998) spectra.

Molecular genetic studies paint a broadly similar picture. For example, a recent meta-analysis of genome-wide association studies (GWAS) of *DSM* generalized anxiety disorder, panic, agoraphobia, social anxiety, and specific phobia identified common variants associated with a higher order anxiety factor, consistent with the HiTOP fear subfactor (Otowa et al., 2016). Other research has investigated behavioral disinhibition (McGue et al., 2013)—an important aspect of the disinhibitory subdomain of the HiTOP externalizing spectrum—and the *p*-factor (Neumann et al., 2016) using both GWAS and genome-wide complex trait analysis (GCTA). In the latter case, results have indicated that single nucleotide polymorphism (SNP)-based heritability of the super-spectrum was moderate (38%), indicating that common autosomal SNPs are associated with a general psychopathology factor in childhood. Beyond these broader spectra, several molecular genetic studies have focused on constructs at the subordinate level of the HiTOP hierarchy, partly to reduce phenotypic heterogeneity and amplify genetic signals. For example, one GWAS investigated a narrowly defined phenotype of mood instability, which led to a discovery of four new genetic variants implicated in mood disorders (Ward et al., 2017). Together, these results suggest that it will be possible to identify specific genetic variants at each level of HiTOP, with some influencing nonspecific psychopathology risk and others conferring risk for individual spectra, subfactors, or even symptoms (e.g., anhedonia). In contrast, traditional case-control study designs are incapable of untangling such hierarchical effects. In short, HiTOP provides a more effective framework for discovering the genetic underpinnings of mental illness.

Neurobiology. Paralleling the genetics literature, there is growing evidence that many measures of brain structure and function do not respect the boundaries implied by traditional *DSM*/*ICD* diagnoses. There are no clear-cut depression or schizophrenia "centers" in the brain (e.g., Sprooten et al., 2017). Instead, associations between the brain and mental illness often show one-to-many or many-to-many relations (i.e., multifinality; Zald & Lahey, 2017). Heightened amygdala reactivity, for example, has been shown to confer risk for the future emergence of mood and anxiety symptoms, posttraumatic distress, and alcohol abuse (e.g., McLaughlin et al., 2014; Swartz, Knodt, Radtke, & Hariri, 2015). The internalizing and externalizing spectra are both associated with altered maturation of subcortical structures in late childhood (Muetzel et al., 2018). In some cases, these relations have been shown to reflect specific symptoms that cut across *DSM's* categorical diagnoses. For instance, anhedonia is a central feature of both mood and thought disorders in *DSM*, and dimensional measures of anhedonia have been linked to aberrant ventral striatum function (i.e., activity and functional connectivity) in several large-scale, mixed-diagnosis studies (Sharma et al., 2017; Stringaris et al. 2015).

Evidence of one-to-many relations is not limited to the neuroimaging literature. The P3 event-related potential (ERP), for example, has been linked to a variety of externalizing disorders and to dimensional measures of externalizing (Iacono, Malone & McGue, 2003; Nelson, Patrick & Bernat, 2011; Patrick et al., 2006). Cross-sectional and prospective studies have linked the error-related negativity (ERN) to a variety of *DSM* anxiety disorders, to the development of internalizing symptoms, and to dimensional measures of anxiety (Cavanagh & Shackman, 2015; Meyer, 2017).

Although the neural bases of the *p*-factor remain far from clear, recent neuroimaging research has begun to reveal some neural systems with conspicuously similar (i.e., general) features. In a recent meta-analysis, McTeague and colleagues (2017) identified a pattern of aberrant activation shared by the major mental disorders. When performing standard cognitive control tasks

(e.g., Go/No-Go, Stroop), patients diagnosed with *DSM* anxiety disorders, bipolar disorder, depression, schizophrenia, or substance abuse all exhibited reduced activation in parts of the so-called salience network, including regions of the cingulate, insular, and prefrontal cortices. Applying a similar approach to voxel-by-voxel measures of brain structure, Goodkind and colleagues (2015) identified a neighboring set of regions in the midcingulate and insular cortices showing a common pattern of cortical atrophy across patients diagnosed with a range of *DSM* disorders (anxiety, bipolar disorder, depression, obsessive-compulsive, and schizophrenia). Few disorder-specific effects were detected in either of these large meta-analyses.

More recent imaging research has begun to adopt the kinds of analytic tools widely used in psychometric and genetic studies of psychopathology, enabling a direct comparison of different levels of HiTOP (cf. Figure 2a) and new clues about the neural bases of the *p*-factor. Using data acquired from the Philadelphia Neurodevelopmental Cohort, Shanmugan and colleagues (2016) identified the *p*-factor and four nested sub-dimensions (antisocial behavior, distress, fear, and psychosis; cf. Figure 1, subfactor level). Higher levels of the *p*-factor were associated with reduced activation and aberrant multivoxel patterns of activity in the salience network (cingulate and insular cortices) during the performance of the n-back task, a widely used measure of working memory capacity and executive function. After accounting for the phenotypic variance explained by the *p*-factor, the antisocial, distress, and psychosis dimensions were each associated with additional subfactor-specific alterations in task-evoked activation (e.g., psychosis was uniquely associated with hypoactivation of the dorsolateral prefrontal cortex). Using the same sample, Kaczkurkin and colleagues (in press) found an analogous pattern of results with measures of resting activity. These observations converge with the meta-analytic results discussed above (Goodkind et al., 2015; McTeague et al., 2017) and reinforce the idea that a circuit centered on the cingulate cortex underlies a range of common psychiatric symptoms and syndromes. Still, it

implausible that this circuit will completely explain a phenotype as broad as the *p*-factor. Indeed, other correlates have already been identified (Sato et al., 2016; Snyder, Hankin, Sandman, Head, & Davis, 2017).

Collectively, these results highlight the unique value of the HiTOP framework for organizing neurobiological research. Adopting a hierarchical dimensional approach makes it possible to dissect brain structure and function quantitatively, enabling the discovery of features that are common to many or all of the common mental disorders, those that are particular to specific spectra and syndromes, and those that underlie key transdiagnostic symptoms—a level of insight not afforded by RDoC or traditional diagnosis-centered nosologies.

Environmental Risk. Stressful environments are intimately intertwined with risk for mental illness. For decades, researchers have proposed theories about the connections between stressors and specific diagnoses (e.g., loss and *DSM* major depression). Yet it is clear that most stressors are non-specific and confer increased risk for diverse psychopathologies. Socioeconomic adversity, discrimination, and harsh parenting all confer widespread risk for psychological problems (Moffitt, 1993; Lehavot & Simoni, 2011; Wiggins, Mitchell, Hyde, & Monk, 2015). The generality of associations for these adversity variables raises the possibility that many stressors act on illness processes that are shared across entire subfactors (e.g., distress, antisocial behavior), spectra (e.g., internalizing), or even super-spectra, rather than specific *DSM* diagnoses. Investigators can use HiTOP to identify the level or levels where stressful environments exert their effects.

Childhood maltreatment represents an instructive case in point because it has potent and non-specific relations with future psychopathology (Green et al., 2010). Several studies have used a hierarchical approach to assess the relative importance of higher order (i.e., transdiagnostic) versus diagnosis-specific pathways from early maltreatment to mental disorders in adulthood. Leveraging interview-based diagnoses and retrospective reports of childhood maltreatment collected as part of

the National Epidemiological Survey on Alcohol and Related Conditions (n > 34,000), Keyes and colleagues observed strong relations between childhood maltreatment and the internalizing and externalizing spectra (cf. path *c* in Figure 3) in the absence of direct associations with specific diagnoses (cf. path *a* in Figure 3) (Keyes et al., 2012). In other words, the marked impact of childhood maltreatment on adult psychopathology was fully mediated by the transdiagnostic spectra. Similar findings emerged in a community sample of over 2,000 youth overselected for maltreatment (Vachon, Krueger, Rogosch, & Cicchetti, 2015; see also Conway, Raposa, Hammen, & Brennan, 2018; Lahey et al., 2012; Meyers et al., 2015; Sunderland et al., 2016).

The HiTOP framework has also been used to understand the influence of chronic stressors in adulthood (Snyder, Young, & Hankin, 2017). For instance, Rodriguez-Seijas et al. (2015) recently showed that racial discrimination has strong associations with the internalizing and externalizing spectra (cf. path *c* in Figure 3) in a nationally representative sample of over 5,000 Black Americans. For most disorders, the pathway from discrimination to particular *DSM* diagnoses (e.g., ADHD, social phobia) was largely explained by its impact on higher order spectra. In a few cases, discrimination was directly associated with specific diagnoses (e.g., alcohol use disorder). These effects make it clear that multiple pathways from environmental adversity to psychopathology are possible—some centered on transdiagnostic spectra, others on more specific syndromes—with important implications for efforts to develop more effective prevention and treatment strategies.

Clinical Outcome Research from a HiTOP Perspective

Like etiological factors, clinical outcomes often reflect a mixture of specific and transdiagnostic effects and, as a result, are better aligned with HiTOP than traditional nosological systems, like the *DSM* or *ICD*.

Prognosis. Clinicians and researchers often seek to forecast the onset (or recurrence) of psychological problems based on diagnostic and symptom data (e.g., Morey et al., 2012). The HiTOP system has the potential to streamline this prognostic decision-making. For instance, using data gleaned from the World Mental Health Surveys (N > 20,000), Kessler et al. (2011) examined the prognostic value of 18 *DSM-IV* disorders in predicting new onsets of subsequent diagnoses. They found that the vast majority of the development of categorical diagnoses arising at later time points was attributable to variation on higher order internalizing and externalizing dimensions earlier in life (for similar results, see Eaton et al., 2013). This result suggests that higher order dimensions provide a more efficient means of predicting the natural course of mental illness (see also Kotov, Perlman, Gamez, & Watson, 2015; Olino et al., in press).

Suicide. The HiTOP model has also proven useful for optimizing suicide prediction. Tools for forecasting suicide are often based on the presence or absence of specific *DSM* diagnoses (e.g., bipolar disorder, borderline personality disorder). But recent large-scale studies have consistently shown that the predictive power of specific *DSM* diagnoses pales in comparison to that of higher order dimensions. For instance, in the NESARC sample described earlier, the distress subfactor (Figure 1) explained ~34% of the variance in suicide attempt history. In contrast, the top-performing *DSM* diagnoses only accounted for ~1% (Eaton et al., 2013; see also Naragon-Gainey & Watson, 2011; Sunderland & Slade, 2015). These kinds of observations indicate that suicide risk is better conceptualized at the level of spectra, not syndromes, contrary to standard research and clinical practices.

Impairment. Psychosocial impairment is typically a core feature of psychopathology, and it often persists long after acute symptoms have abated. Understanding impairment is important for prioritizing scarce resources. But is impairment better explained and, more importantly, predicted by *DSM/ICD* diagnoses or transdiagnostic dimensions? Using data from the Collaborative

Longitudinal Personality Disorders Study (N = 668), Morey et al. (2012) found that maladaptive personality traits were twice as effective at predicting functional impairment across a decade-long follow-up, when compared to traditional diagnoses (cf. Figure 2c). Likewise, Forbush and colleagues demonstrated that higher order dimensions explain 68% of the variance in impairment in a sample of adult patients with eating pathology (Forbush et al., 2017). In contrast, *DSM*-derived anxiety, depression, and eating disorder diagnoses collectively explained only 11%. In the area of psychosis, van Os and colleagues (1999) compared the predictive power of five dimensions versus eight *DSM* diagnoses in a large longitudinal sample across 20 distinct psychosocial outcomes (e.g., disability, unemployment, cognitive impairment, and suicide). For every outcome with a clear difference in predictive validity, dimensions outperformed diagnoses.

Waszczuk, Kotov, et al. (2017) reported similar results in two samples evaluated with the Interview for Mood and Anxiety Symptoms (IMAS), which assesses the lower order components of emotional pathology (e.g., lassitude, obsessions). They found that lower order internalizing dimensions jointly explained nearly two times more variance in functional impairment than *DSM* diagnoses. Moreover, *DSM* diagnoses jointly did not show any incremental power over the dimensions' scores—a particularly striking result given that impairment is usually part of *DSM* diagnostic criteria but not of IMAS scores (cf. Figure 2c). In sum, this line of research suggests that transdiagnostic dimensions of the kinds embodied in HiTOP have superior prognostic value—both concurrently and prospectively—for psychosocial impairment (see also Jonas & Markon, 2013; Markon, 2010; South, Krueger, & Iacono, 2011).

Summary

Traditionally, theoretical models of the causes and consequences of psychiatric problems have been framed around diagnoses. New research highlights the importance of extending this focus to encompass transdiagnostic dimensions, including both narrowly defined symptoms and

traits (e.g., anhedonia) and broader clusters of psychological conditions (e.g., internalizing spectrum). Unlike other classification systems (e.g., *DSM*) and unlike RDoC, HiTOP provides a framework for rigorously testing the relative importance of symptom components, syndromes, spectra, and super-spectra (e.g., *p*-factor) for the emergence and treatment of psychopathology (Figure 1). The evidence that we have reviewed suggests that in many cases (but perhaps not all) mental illness is better conceptualized in terms of transdiagnostic dimensions.

HiTOP: A Practical Guide

A primary objective of this review is to provide investigators with some practical recommendations for incorporating HiTOP into their research. Here we outline research design, assessment, and analytic strategies that follow from the theory and available data underpinning the HiTOP model.

Design. Historically, the lion's share of clinical research has been conducted using traditional *case-control designs*, in which participants meeting criteria for a particular diagnosis of interest are compared to a group free of that disorder (or of *any* mental illness). This approach is generally inconsistent with a dimensional perspective on psychopathology. There is overwhelming evidence that mental illness is continuously distributed in the population, without the gaps or "zones of discontinuity" expected of categorical illnesses (Krueger et al., in press; although for a different perspective see Borsboom et al., 2016). This evidence indicates that an appreciable loss of information results from artificially separating cases from non-cases (Markon et al., 2011), consistent with more general recommendations to eschew post hoc dichotomization (e.g., median splits) of naturally continuous processes in psychology research broadly (Preacher, Rucker, MacCallum, & Nicewander, 2005).

The case-control recruitment strategy also ignores problems stemming from ubiquitous diagnostic comorbidity. Such co-occurrence among disorders has made it virtually impossible to

establish discriminant validity for most categorical syndromes. In practical terms, any distinction observed between, for example, *DSM* panic disorder patients and healthy controls in a given research study may not be a unique characteristic of panic disorder. Instead, an observed group effect may reflect the influence of some higher order dimension of psychopathology (e.g., fear subfactor) that permeates multiple related *DSM* diagnoses (e.g., panic disorder, agoraphobia, social anxiety disorder, and specific phobia). By disregarding the symptom overlap among clusters of related conditions, the case-control design is bound to underestimate the breadth of psychopathology associated with a given clinical outcome.

From an efficiency standpoint, recruiting on the basis of single disorder categories creates an unnecessarily fragmented scientific record. The traditional approach of studying one disorder in relation to one outcome has spawned many insular literatures, which belies the commonalities among disorders and has led to piecemeal research progress in many areas of mental health research. For example, the initial phases of psychiatric genetic research were oriented around specific diagnoses. There were separate studies into the molecular genetic origins of *DSM*/*ICD* obsessive-compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, and so on. Analogously, there are voluminous literatures on childhood maltreatment in relation to various individual syndromes. These lines of research have consumed vast resources, but they have revealed little in the way of one-to-one associations between risk factors and categorical disorders. A more parsimonious and efficient approach is to recruit participants to a study on the basis of a particular psychopathological dimension (e.g., antisocial behavior, excitement seeking), either sampling to ensure strong representation of all ranges of this dimension, or recruiting at random from the population of interest (e.g., local community, undergraduates, or outpatients) to provide a representative sample. (Incidentally, this is roughly the same recruitment strategy that is recommended under RDoC.) Then, as was the case for our fictional study of autonomic

disruptions in social phobia, the effects of both broad and more specific dimensions of psychopathology can be compared empirically. Thinking broadly, such a strategy promises to facilitate more cumulative, rapid progress in developing etiological models for a wide range of psychological conditions.

It merits comment that some of these design recommendations can be addressed post hoc. Many of the analyses that we have reviewed were carried out using datasets that were not assembled with HiTOP in mind. However, these projects have generally included a thorough assessment of psychopathology outcomes, which can serve as building blocks for quantitative investigations of symptom or syndrome co-occurrence via factor analysis. For example, there have been several studies of the correlates (e.g., demographic features, racial discrimination, childhood maltreatment) of higher order dimensions versus syndromes in epidemiological studies, such as the National Comorbidity Survey-Replication and NESARC (e.g., Eaton et al., 2013; Keyes et al., 2012; Slade, 2007). Investigators have also taken advantage of comprehensive psychopathology assessments in longitudinal cohort studies—such as the Dunedin Multidisciplinary Health and Development Study and the Pittsburgh Girls Study—to examine the temporal course and longitudinal correlates of HiTOP dimensions (e.g., Krueger et al., 1998; Lahey et al., 2015; McElroy, Belsky, Carragher, Fearon, & Patalay, in press). These cohort studies are particularly valuable for theory building because they tend to have rich assessments of validators (etiological factors, clinical outcomes; e.g., Caspi et al., 2014). One consideration is that these datasets tend to be fairly large, compared to case-control studies, which frequently adopt the more statistically powerful (but interpretatively more ambiguous) extreme groups approach (e.g., Preacher et al., 2005).

Assessment. Although assessing multiple syndromic or symptom constructs in the same study represents an improvement over “one disorder, one outcome” designs, there are limitations to

this approach. *DSM* diagnoses and many symptom measures are notoriously heterogeneous, meaning they are composed of multiple lower order dimensions of psychopathology. For instance, many common depressive symptom scales include not only cognitive and vegetative symptoms, which arguably have separate etiologies and correlates, but also include anxiety symptoms (e.g., Fried, 2017). Thus, a more optimal assessment approach is to forego traditional diagnostic constructs in favor of homogeneous lower order dimensions of pathology (e.g., the symptom component level of Figure 1). This strategy maximizes the precision of the dimensions that can be examined, improving our ability to "carve nature at its joints."

Consequently, we strongly recommend transdiagnostic assessment instruments that measure both higher and lower order transdiagnostic dimensions of psychopathology. A number of such measures are reviewed in Kotov et al. (2017). No omnibus inventory yet exists that covers the entirety of the HiTOP framework, although our consortium is currently developing one. Instead, there are many existing measures that assess specific aspects (e.g., component/trait, syndrome, and subfactor levels) of the HiTOP model (see https://psychology.unt.edu/hitop). Researchers can use these measures to perform a complete assessment of one spectrum (e.g., antagonistic externalizing) or several (e.g., antagonistic externalizing, disinhibited externalizing, thought disorder). The list of measures is expected to continue evolving, and researchers can refer to the HiTOP website listed above to access the latest inventories, including a forthcoming comprehensive measure of the full HiTOP model, as currently constituted. At present, most facets of the HiTOP structure can be assessed economically with questionnaire measures that are available in self- and informant-report versions, although structured and semi-structured interview approaches can also be used, assuming the interviews allow for dimensional scoring. Regarding interviews, we note that for assessments to be compatible with a dimensional approach, researchers must modify them to eliminate "skip rules" (e.g., if neither significant depressed mood or anhedonia is endorsed, some interview

procedures automatically exit the major depression section) and hierarchical decision rules (e.g., *DSM-IV* stipulated that generalized anxiety disorder could not be diagnosed if it presented only in the context of a co-occurring depressive disorder) in order to collect all symptom data. Overriding these rules permits assessment of the full clinical picture, unconstrained by historical conventions that almost surely do not reflect the nature of psychopathology.

Analysis. There are several different ways for investigators to test the association of dimensional constructs with outcomes of interest. Expertise with latent variable modeling is not a prerequisite. Many popular measurement tools (e.g., the Child Behavior Checklist; Achenbach, 1991) include both broadband (e.g., externalizing) and narrower (e.g., aggression) dimensions. Connections of these scales with background characteristics or clinical outcomes could then be contrasted using standard regression approaches.

In some cases, it is possible to use latent variable modeling to extract the relevant dimensions from the data empirically. Exploratory factor analysis (EFA) is a useful technique for deriving latent dimensions. EFA is an atheoretical approach to determining the appropriate number and nature of latent dimensions undergirding psychological problems. In many common statistical packages, it is possible to perform an EFA and then extract factor scores—values that represent a person's standing on a latent dimension—that can be used as variables in standard regression or analysis of variance procedures (although this procedure has some drawbacks; e.g., Devlieger, Mayer, & Rosseel, 2016). Confirmatory factor analysis, a hypothesis-driven approach in which the researcher specifies the relations of symptom or diagnostic constructs to latent dimensions, is another common approach in this area. Finally, Goldberg's (2006) approach of using a series of factor analyses to explicate a hierarchical factor structure, by proceeding from higher (broader) to lower (narrower) levels of specificity (termed the "bass-ackwards" method), can be useful in extracting HiTOP dimensions from symptom- or diagnostic-level data.

Future Challenges

It is clear that there are compelling scientific reasons to adopt HiTOP-style approaches to understanding psychopathology. But it is equally clear that additional work will be required to refine this framework and its role in research on mental illness. Uncertainties remain about several architectural elements of HiTOP. Additional research is needed to incorporate psychiatric problems not currently included in HiTOP (e.g., autism spectrum disorder and other neurodevelopmental conditions) and to validate the placement of domains of psychopathology that have received limited attention in structural studies (e.g., mania as a component of internalizing versus thought disorder). At the spectrum level, data are particularly limited for HiTOP's somatoform and detachment dimensions. Thus, the system is a work in progress and researchers are encouraged to consult the consortium website for updates or to apply for membership in the consortium and contribute to improving the model.

Moving forward, we also need to examine carefully the use and interpretation of factor analysis with respect to HiTOP. There are questions about whether the theoretical constructs outlined in HiTOP satisfy assumptions of the common factor model (e.g., van Bork, Epskamp, Rhemtulla, Borsboom, & van der Maas, 2017; see also Borsboom, Mellenbergh, & van Heerden, 2003). For instance, are the factors (e.g., fear, detachment) naturally occurring phenomena that directly cause variation in their indicators (e.g., panic, social phobia)? Or are the HiTOP factors simply useful—and, to some extent, artificial—summaries of symptom covariation (see Jonas & Markon, 2016)? We note that although factor analysis has proved to be a useful tool in this area of research, HiTOP outcomes need not be represented by latent variables; it is possible to operationalize them directly using questionnaire and interview measures of the types mentioned earlier, although every specific measure has strengths, weakness, and a particular range of applicability, so it will be important not to equate measures with constructs.

Over the coming years, research will be needed on the compatibility between HiTOP and two other popular conceptualizations of mental illness: network models and RDoC (e.g., Clark et al., 2017). Network models conventionally assume that latent traits *do not* cause symptom clustering, and that psychological syndromes instead arise from a chain reaction of symptoms directly activating one another (e.g., Cramer, Waldorp, van der Maas, & Borsboom, 2010). A common example is that a constellation of depression symptoms might coalesce not because of the guiding influence of an unobserved, unitary depression dimension, but rather due to a "snowballing" *sequence* of symptom development (e.g., insomnia > fatigue, fatigue > concentration problems, and so on). The purpose of the network model is to discern these hypothesized causal pathways among symptoms. In contrast, HiTOP aims to identify replicable clusters of symptoms that have shared risk factors and outcomes. Both perspectives can be useful for understanding the nature of psychopathology and are not necessarily mutually exclusive (e.g., Fried & Cramer, 2017).

The RDoC initiative, like HiTOP, seeks to deconstruct psychopathology into more basic units (cf. lower level of Figure 1). RDoC proponents theorize that it is easier to trace the genetic and neurobiological causes of these more homogeneous—and presumably less etiologically complex—units, or intermediate phenotypes (Cuthbert & Insel, 2013). The RDoC matrix also appears to prioritize biological mechanisms of mental illness, explicitly conceptualizing mental illness as "brain disorders" or "neural circuit disorders" (e.g., Insel & Cuthbert, 2015), although the matrix has three non-brain, biobehavioral units and the entire matrix is embedded in the psychosocial cultural environment (see Clark et al., 2017, Figure 1). One of the goals of RDoC is to provide a framework for examining how biological processes will be connected to observable, clinically relevant psychopathology. HiTOP therefore represents an important complement to the RDoC system by providing a quantitative classification of the outward (i.e., phenotypic) signs and

symptoms of mental illness. That is, these two approaches could be integrated to delineate the pathophysiology of clinically relevant pathology (e.g., Krueger et al., in press).

The most important avenue for future empirical work, in our view, is continued validation research into the nature and utility of the dimensions that make up the HiTOP model. In particular, validation studies to date have been mostly limited to the spectrum level (e.g., correlates of internalizing, disinhibited externalizing), and criterion validity research is needed at other levels of the hierarchy. Also, existing research has largely relied on snapshots of symptoms and syndromes without modeling illness course. Developmental studies that are equipped to examine the longitudinal correlates of HiTOP dimensions are a pressing priority (cf. Lahey et al., 2015; Wright, Hopwood, Skodol, & Morey, 2016).

Future research is also required to clarify whether and how HiTOP can advance research on psychological treatment. There are some preliminary indications that treatment decisions—both on the part of patients (Rodriguez-Seijas, Eaton, Stohl, Mauro, & Hasin, 2017) and clinicians (Waszczuk, Zimmerman et al., 2017)—tend to be based substantially on transdiagnostic difficulties (e.g., thought problems) rather than particular categorical diagnoses (e.g., schizoaffective disorder). Further, there is emerging evidence that transdiagnostic psychotherapies can be as effective as traditional treatments that target only one disorder. For example, the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (Barlow et al., 2014) was developed to address common temperamental processes theorized to lie at the core of internalizing problems. Rather than using separate protocols to treat individual *DSM* diagnoses, such as major depression and generalized anxiety disorder, the Unified Protocol uses cognitive-behavioral strategies to reduce negative emotionality and increase positive emotionality, traits thought to maintain anxiety and depression over time (Barlow et al., 2017). Practitioners can apply the Unified Protocol to a diverse set of anxiety and depressive conditions, streamlining the training process and minimizing barriers

to dissemination, as compared to standard training models that involve learning a separate treatment framework for each *DSM* disorder. The policy of using one psychological treatment for various conditions is analogous to standard prescription practices for psychiatric medications, which often work across—and in many cases have regulatory approval for treatment of—multiple diagnostic categories.

Conclusion

There is now compelling evidence that the nature of psychopathology is dimensional and hierarchical, with many studies indicating that genes, neurobiology, and clinical outcomes align with this new conceptualization. We recommend a shift in mental health research practices to match the HiTOP model. This emerging system has the potential to (i) expand existing theories and generate new hypotheses; (ii) unify empirical literatures (e.g., unnecessarily fragmented lines of evidence on marital dysfunction in posttraumatic stress disorder, alcohol use disorder, antisocial personality disorder, etc.); (iii) increase the utility of classification systems for both basic and applied research; and (iv) establish novel phenotypes that explain the etiology of psychological problems and serve as more efficient assessment and treatment targets.

Research on the utility of transdiagnostic dimensions of psychopathology remains in its early stages, but the future seems promising. If validated, this system has the potential to transform research practices for the better and accelerate theory development across diverse fields in psychological science.

References

Achenbach, T. M. (1991). *Manual for the child behavior checklist/4-18 and 1991 profile*. Burlington: University of Vermont, Department of Psychiatry.

Achenbach, T. M. (1966). The classification of children's psychiatric symptoms: A factor-analytic study. Psychological Monographs, 80, 1-37.

Barlow, D. H., Farchione, T. J., Bullis, J. R., Gallagher, M. W., …, & Cassiello-Robbins, C. (2017). The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders compared with diagnosis-specific protocols for anxiety disorders: A randomized clinical trial. *JAMA Psychiatry, 74*, 875-884.

Barlow, D. H., Sauer-Zavala, S., Carl, J. R., Bullis, J. R., & Ellard, K. K. (2014). The nature, diagnosis, and treatment of neuroticism: Back to the future. *Clinical Psychological Science, 2*, 344-365.

Borsboom, D., Mellenbergh, G. J., & Van Heerden, J. (2003). The theoretical status of latent variables. *Psychological Review, 110*, 203-219.

Borsboom, D., Rhemtulla, M., Cramer, A. O. J., van der Maas, H. L. J., Scheffer, M., & Dolan, C. V. (2016). Kinds versus continua: a review of psychometric approaches to uncover the structure of psychiatric constructs. *Psychological Medicine*, 1-13.

Brown, T. A., & Barlow, D. H. (2009). A proposal for a dimensional classification system based on the shared features of the DSM-IV anxiety and mood disorders: Implications for assessment and treatment. *Psychological Assessment, 21*, 256-271.

Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., . . . Moffitt, T. E. (2014). The *p* factor: One general psychopathology factor in the structure of psychiatric disorders? *Clinical Psychological Science, 2*, 119-137.

Caspi, A., & Moffitt, T. E. (in press). All for one and one for all: Mental disorders in one dimension. *American Journal of Psychiatry*.

Cavanagh, J. F., & Shackman, A. J. (2015). Frontal midline theta reflects anxiety and cognitive control: Meta-analytic evidence. *Journal of Physiology, 109,* 3-15.

Clark, L. A., Cuthbert, B., Lewis-Fernández, R., Narrow, W. E., & Reed, G. M. (2017). Three Approaches to Understanding and Classifying Mental Disorder: ICD-11, DSM-5, and the National Institute of Mental Health's Research Domain Criteria (RDoC). *Psychological Science in the Public Interest, 18,* 72-145.

Cramer, A. O., Waldorp, L. J., van der Maas, H. L., & Borsboom, D. (2010). Complex realities require complex theories: Refining and extending the network approach to mental disorders. *Behavioral and Brain Sciences, 33,* 178-193.

Conway, C. C., Hammen, C., & Brennan, P. A. (2012). Expanding stress generation theory: Test of a transdiagnostic model. *Journal of Abnormal Psychology, 121,* 754-766.

Conway, C. C., Raposa, E. B., Hammen, C., & Brennan, P. A. (2018). Transdiagnostic pathways from early social stress to psychopathology: a 20-year prospective study. *Journal of Child Psychology and Psychiatry*.

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: The seven pillars of RDoC. *BMC Medicine, 11,* 126-134.

Devlieger, I., Mayer, A., & Rosseel, Y. (2016). Hypothesis testing using factor score regression: A comparison of four methods. *Educational and Psychological Measurement, 76,* 741-770.

DiLuca, M., & Olesen, J. (2014). The cost of brain diseases: a burden or a challenge?. *Neuron, 82,* 1205-1208.

Eaton, N. R., Krueger, R. F., Markon, K. E., Keyes, K. M., Skodol, A. E., Wall, M., . . . Grant, B. F. (2013). The structure and predictive validity of the internalizing disorders. *Journal of Abnormal Psychology, 122,* 86-92.

Eysenck, H. J. (1944). Types of personality: a factorial study of seven hundred neurotics. *The British Journal of Psychiatry, 90,* 851-861.

Forbes, M. K., Tackett, J. L., Markon, K. E., & Krueger, R. F. (2016). Beyond Comorbidity: Toward a dimensional and hierarchal approach to understanding psychopathology across the lifespan. *Development and Psychopathology, 28,* 971-986.

Forbush, K. T., Hagan, K. E., Kite, B. A., Chapa, D. A., Bohrer, B. K., & Gould, S. R. (2017). Understanding eating disorders within internalizing psychopathology: A novel transdiagnostic, hierarchical-dimensional model. *Comprehensive Psychiatry, 79,* 40-52.

Fried, E. I. (2017). The 52 symptoms of major depression: Lack of content overlap among seven common depression scales. *Journal of Affective Disorders, 208,* 191-197.

Fried, E. I., & Cramer, A. O. J. (2017). Moving forward: Challenges and directions for psychopathological network theory and methodology. *Perspectives on Psychological Science, 12,* 999-1020.

Goldberg, L. R. (2006). Doing it all bass-ackwards: The development of hierarchical factor structures from the top down. *Journal of Research in Personality, 40,* 347-358.

Goodkind, M., Eickhoff, S. B., Oathes, D. J., Jiang, Y., Chang, A., Jones-Hagata, L. B., . . ., Etkin, A. (2015). Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry, 72,* 305-315.

Green, J. G., McLaughlin, K. A., Berglund, P. A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood adversities and adult psychiatric disorders in the

national comorbidity survey replication I: Associations with first onset of DSM-IV disorders. *Archives of General Psychiatry, 67,* 113-123.

Hammen, C. (1991). Generation of stress in the course of unipolar depression. *Journal of Abnormal Psychology, 100,* 555-561.

Iacono, W. G., Malone, S. M., & McGue, M. (2003). Substance use disorders, externalizing psychopathology, and P300 event-related potential amplitude. *International Journal of Psychophysiology, 48,* 147-178.

Insel, T. R., & Cuthbert, B. N. (2015). Brain disorders? Precisely. *Science, 348,* 499-500.

Hyman, S. E. (2007). Can neuroscience be integrated into the DSM-V?. *Nature Reviews Neuroscience, 8,* 725-732.

Jonas, K. G., & Markon, K. E. (2013). A model of psychosis and its relationship with impairment. *Social Psychiatry and Psychiatric Epidemiology, 48,* 1367-1375.

Jonas, K. G., & Markon, K. E. (2016). A descriptivist approach to trait conceptualization and inference. *Psychological Review, 123,* 90-96.

Kaczkurkin, A. N., Moore, T. M., Calkins, M. E., Ciric, R., Detre, J. A., Elliott, M. A., ... & Ruparel, K. (in press). Common and dissociable regional cerebral blood flow differences associate with dimensions of psychopathology across categorical diagnoses. *Molecular Psychiatry*.

Kendler, K. S., Aggen, S. H., & Neale, M. C. (2013). Evidence for multiple genetic factors underlying DSM-IV criteria for major depression. *JAMA Psychiatry, 70,* 599-607.

Kendler, K. S., & Myers, J. (2014). The boundaries of the internalizing and externalizing genetic spectra in men and women. *Psychological Medicine, 44,* 647-655.

Kessler, R. C., Petukhova, M., & Zaslavsky, A. M. (2011). The role of latent internalizing and externalizing predispositions in accounting for the development of comorbidity among common mental disorders. *Current Opinion in Psychiatry, 24*, 307-312.

Keyes, K. M., Eaton, N. R., Krueger, R. F., McLaughlin, K. A., Wall, M. M., Grant, B. F., & Hasin, D. S. (2012). Childhood maltreatment and the structure of common psychiatric disorders. *The British Journal of Psychiatry, 200,* 107-115.

Kotov, R., Krueger, R. F., Watson, D., Achenbach, T. M., Althoff, R. R., Bagby, R. M., ... & Zimmerman, M. (2017). The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *Journal of Abnormal Psychology, 126,* 454-477.

Kotov, R., Perlman, G., Gámez, W., & Watson, D. (2015). The structure and short-term stability of the emotional disorders: a dimensional approach. *Psychological Medicine, 45,* 1687-1698.

Krueger, R. F., Caspi, A., Moffitt, T. E., & Silva, P. A. (1998). The structure and stability of common mental disorders (DSM-III-R): A longitudinal-epidemiological study. *Journal of Abnormal Psychology, 107,* 216-227.

Krueger, R. F., Kotov, R., Watson, D., Forbes, M. K., Eaton, N. R., Ruggero, C. J., ... Zimmermann, J. (in press). Progress in achieving quantitative classification of psychopathology. *World Psychiatry*.

Lahey, B.B., Applegate, B., Hakes, J.K., Zald, D.H., Hariri, A.R., & Rathouz, P.J. (2012). Is there a general factor of prevalent psychopathology during adulthood? *Journal of Abnormal Psychology, 121,* 971-977.

Lahey, B. B., Krueger, R. F., Rathouz, P. J., Waldman, I. D., & Zald, D. H. (2017). A hierarchical causal taxonomy of psychopathology across the life span. *Psychological Bulletin, 143,* 142-186.

Lahey, B. B., Rathouz, P. J., Keenan, K., Stepp, S. D., Loeber, R., & Hipwell, A. E. (2015). Criterion validity of the general factor of psychopathology in a prospective study of girls. *Journal of Child Psychology and Psychiatry, 4,* 415-422.

Lehavot, K., & Simoni, J. M. (2011). The impact of minority stress on mental health and substance use among sexual minority women. *Journal of Consulting and Clinical Psychology, 79,* 159.

Livesley, W. J., Jang, K. L., & Vernon, P. A. (1998). Phenotypic and genetic structure of traits delineating personality disorder. *Archives of General Psychiatry, 55,* 941-948.

Liu, R. T., & Alloy, L. B. (2010). Stress generation in depression: A systematic review of the empirical literature and recommendations for future study. *Clinical Psychology Review, 30,* 582-593.

Markon, K. E. (2010). Modeling psychopathology structure: A symptom-level analysis of Axis I and II disorders. *Psychological Medicine, 40,* 273-288.

Markon, K. E., Chmielewski, M., & Miller, C. J. (2011). The reliability and validity of discrete and continuous measures of psychopathology: a quantitative review. *Psychological Bulletin, 137,* 856.

McElroy, E., Belsky, J., Carragher, N., Fearon, R. M. P., & Patalay, P. (in press). Developmental stability of general and specific factors of psychopathology from early childhood through adolescence: Dynamic mutualism or p-differentiation?. *Journal of Child Psychology and Psychiatry*.

McGue, M., Zhang, Y., Miller, M. B., Basu, S., Vrieze, S., Hicks, B., ... & Iacono, W. G. (2013). A genome-wide association study of behavioral disinhibition. *Behavior Genetics, 43,* 363-373.

McLaughlin, K. A., Busso, D. S., Duys, A., Green, J. G., Alves, S., Way, M., & Sheridan, M. A. (2014). Amygdala response to negative stimuli predicts PTSD symptom onset following a terrorist attack. *Depression and Anxiety, 31,* 834-842.

McTeague, L. M., Huemer, J., Carreon, D. M., Jiang, Y., Eickhoff, S. B., & Etkin, A. (2017). Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. *American Journal of Psychiatry, 174,* 676-685.

Meyer, A. (2017). A biomarker of anxiety in children and adolescents: A review focusing on the error-related negativity (ERN) and anxiety across development. *Developmental Cognitive Neuroscience, 27,* 58-68.

Meyers, J. L., Lowe, S. R., Eaton, N. R., Krueger, R., Grant, B. F., & Hasin, D. (2015). Childhood maltreatment, 9/11 exposure, and latent dimensions of psychopathology: A test of stress sensitization. *Journal of Psychiatric Research, 68,* 337-345.

Moffitt, T. E. (1993). Adolescence-limited and life-course-persistent antisocial behavior: a developmental taxonomy. *Psychological Review, 100,* 674.

Moore, T. V. (1930). The empirical determination of certain syndromes underlying praecox and manic-depressive psychoses. *American Journal of Psychiatry, 86,* 719-738.

Morey, L. C., Hopwood, C. J., Markowitz, J. C., Gunderson, J. G., Grilo, C. M., McGlashan, T. H., . . . Skodol, A. E. (2012). Comparison of alternative models for personality disorders, II: 6-, 8- and 10-year follow-up. *Psychological Medicine, 42,* 1705-1713.

Muetzel, R. L., Blanken, L. M., van der Ende, J., El Marroun, H., Shaw, P., Sudre, G., ... & White, T. (2018). Tracking brain development and dimensional psychiatric symptoms in children: A longitudinal population-based neuroimaging study. *American Journal of Psychiatry, 1,* 54-62.

Naragon-Gainey, K., & Watson, D. (2011). The anxiety disorders and suicidal ideation: accounting for co-morbidity via underlying personality traits. *Psychological Medicine, 41,* 1437-1447.

Nelson, L. D., Patrick, C. J., & Bernat, E. M. (2011). Operationalizing proneness to externalizing psychopathology as a multivariate psychophysiological phenotype. *Psychophysiology, 48,* 64-72.

Neumann, A., Pappa, I., Lahey, B. B., Verhulst, F. C., Medina-Gomez, C., Jaddoe, V. W., ... & Tiemeier, H. (2016). Single nucleotide polymorphism heritability of a general psychopathology factor in children. *Journal of the American Academy of Child & Adolescent Psychiatry, 55,* 1038-1045.

Olino, T. M., Bufferd, S. J., Dougherty, L. R., Dyson, M. W., Carlson, G. A., & Klein, D. N. (in press). The development of latent dimensions of psychopathology across early childhood: stability of dimensions and moderators of change. *Journal of Abnormal Child Psychology*.

Otowa, T., Hek, K., Lee, M., Byrne, E. M., Mirza, S. S., Nivard, M. G., ... & Fanous, A. (2016). Meta-analysis of genome-wide association studies of anxiety disorders. *Molecular psychiatry, 21,* 1391-1399.

Patrick, C. J., Bernat, E. M., Malone, S. M., Iacono, W. G., Krueger, R. F., & McGue, M. (2006). P300 amplitude as an indicator of externalizing in adolescent males. *Psychophysiology, 43,* 84-92.

Pettersson, E., Larsson, H., & Lichtenstein, P. (2016). Common psychiatric disorders share the same genetic origin: A multivariate sibling study of the Swedish population. *Molecular Psychiatry, 21,* 717-721.

Preacher, K. J., Rucker, D. D., MacCallum, R. C., & Nicewander, W. A. (2005). Use of the extreme groups approach: A critical reexamination and new recommendations. *Psychological Methods, 10,* 178-192.

Redish, A. D., & Gordon, J. A. (2016). *Computational psychiatry: New perspectives on mental illness*. MIT Press.

Regier, D. A., Narrow, W. E., Clarke, D. E., Kraemer, H. C., Kuramoto, S. J., Kuhl, E. A., & Kupfer, D. J. (2013). DSM-5 field trials in the United States and Canada, Part II: Test-retest reliability of selected categorical diagnoses. *The American Journal of Psychiatry, 170*, 59-70.

Rodriguez-Seijas, C., Eaton, N. R., Stohl, M., Mauro, P. M., & Hasin, D. S. (2017). Mental disorder comorbidity and treatment utilization. *Comprehensive Psychiatry, 79*, 89-97.

Rodriguez-Seijas, C., Stohl, M., Hasin, D. S., & Eaton, N. R. (2015). Transdiagnostic factors and mediation of the relationship between perceived racial discrimination and mental disorders. *Journal of the American Medical Association Psychiatry, 72*, 706-713.

Rosenström, T., Ystrom, E., Torvik, F. A., Czajkowski, N. O., Gillespie, N. A., Aggen, S. H., . . . Reichborn-Kjennerud, T. (2017). Genetic and environmental structure of DSM-IV criteria for antisocial personality disorder: A twin study. *Behavior Genetics, 47*, 265-277.

Røysamb, E., Kendler, K. S., Tambs, K., Ørstavik, R. E., Neale, M. C., Aggen, S. H., ... & Reichborn-Kjennerud, T. (2011). The joint structure of DSM-IV Axis I and Axis II disorders. *Journal of Abnormal Psychology, 120*, 198-209.

Sato, J. R., Salum, G. A., Gadelha, A., Crossley, N., Vieira, G., Manfro, G. G., . . . Hoexter, M. Q. (2016). Default mode network maturation and psychopathology in children and adolescents. *Journal of Child Psychology and Psychiatry, 57*, 55-64

Shackman, A. J., & Fox, A. S. (2018). Getting serious about variation: Lessons for clinical neuroscience (A commentary on ‘The myth of optimality in clinical neuroscience’). *Trends in Cognitive Sciences, 22*, 368-369.

Shanmugan, S., Wolf, D. H., Calkins, M. E., Moore, T. M., Ruparel, K., Hopson, R. D., ... & Gennatas, E. D. (2016). Common and dissociable mechanisms of executive system dysfunction across psychiatric disorders in youth. *American Journal of Psychiatry*, *173*, 517-526.

Sharma, A., Wolf, D. H., Ciric, R., Kable, J. W., Moore, T. M., Vandekar, S. N., ... & Elliott, M. A. (2017). Common dimensional reward deficits across mood and psychotic disorders: a connectome-wide association study. *American Journal of Psychiatry*, *174*, 657-666.

Simms, L. J., Grös, D. F., Watson, D., & O'Hara, M. W. (2008). Parsing the general and specific components of depression and anxiety with bifactor modeling. *Depression and Anxiety*, *25*, 34-46.

Slade, T. (2007). The descriptive epidemiology of internalizing and externalizing psychiatric dimensions. *Social Psychiatry and Psychiatric Epidemiology*, *42*, 554-560.

Snyder, H. R., Hankin, B. L., Sandman, C. A., Head, K., & Davis, E. P. (2017). Distinct patterns of reduced prefrontal and limbic gray matter volume in childhood general and internalizing psychopathology. *Clinical Psychological Science*, *5*, 1001-1013.

Snyder, H. R., Young, J. F., & Hankin, B. L. (2017). Chronic stress exposure and generation are related to the p-factor and externalizing specific psychopathology in youth. *Journal of Clinical Child and Adolescent Psychology*, 1-10.

South, S. C., Krueger, R. F., & Iacono, W. G. (2011). Understanding general and specific connections between psychopathology and marital distress: A model based approach. *Journal of Abnormal Psychology*, *120*, 935-947.

Sprooten, E., Rasgon, A., Goodman, M., Carlin, A., Leibu, E., Lee, W. H., & Frangou, S. (2017). Addressing reverse inference in psychiatric neuroimaging: Meta-analyses of task-related brain activation in common mental disorders. *Human Brain Mapping*, *38*, 1846-1864.

Stringaris, A., Vidal-Ribas Belil, P., Artiges, E., Lemaitre, H., Gollier-Briant, F., Wolke, S., ... & Fadai, T. (2015). The brain's response to reward anticipation and depression in adolescence: dimensionality, specificity, and longitudinal predictions in a community-based sample. *American Journal of Psychiatry, 172,* 1215-1223.

Sunderland, M., Carragher, N., Chapman, C., Mills, K., Teesson, M., Lockwood, E., ... & Slade, T. (2016). The shared and specific relationships between exposure to potentially traumatic events and transdiagnostic dimensions of psychopathology. *Journal of Anxiety Disorders, 38,* 102-109.

Sunderland, M., & Slade, T. (2015). The relationship between internalizing psychopathology and suicidality, treatment seeking, and disability in the Australian population. *Journal of Affective Disorders, 171,* 6-12.

Swartz, J. R., Knodt, A. R., Radtke, S. R., & Hariri, A. R. (2015). A neural biomarker of psychological vulnerability to future life stress. *Neuron, 85,* 505-511.

Tarbox, S. I., & Pogue-Geile, M. F. (2011). A multivariate perspective on schizotypy and familial association with schizophrenia: a review. *Clinical Psychology Review, 31,* 1169-1182.

Vachon, D.D., Krueger, R.F., Rogosch, F.A., & Cicchetti, D. (2015). Assessment of the harmful psychiatric and behavioral effects of different forms of child maltreatment. *JAMA Psychiatry, 72,* 1135-1142.

van Bork, R., Epskamp, S., Rhemtulla, M., Borsboom, D., & van der Maas, H. L. (2017). What is the p-factor of psychopathology? Some risks of general factor modeling. *Theory & Psychology, 27,* 759-773.

van Os, J., Gilvarry, C., Bale, R., Van Horn, E., Tattan, T., & White, I. (1999). A comparison of the utility of dimensional and categorical representations of psychosis. *Psychological Medicine, 29,* 595-606.

Vos, T., Allen, C., Arora, M., Barber, R. M., Bhutta, Z. A., Brown, A., ... & Coggeshall, M. (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet, 388,* 1545-1602.

Ward, J., Strawbridge, R., Graham, N., Bailey, M., Freguson, A., Lyall, D., ... & Pell, J. (2017). Genome-Wide Analysis Of 113,968 Individuals In UK Biobank Identifies Four Loci Associated With Mood Instability. *bioRxiv*, 117796.

Waszczuk, M. A., Kotov, R., Ruggero, C., Gamez, W., & Watson, D. (2017). Hierarchical structure of emotional disorders: From individual symptoms to the spectrum. *Journal of Abnormal Psychology, 126,* 613.

Waszczuk, M. A., Zavos, H. M. S., Gregory, A. M., & Eley, T. C. (2014). The phenotypic and genetic structure of depression and anxiety disorder symptoms in childhood, adolescence, and young adulthood. *JAMA Psychiatry, 71,* 905-916.

Waszczuk, M. A., Zimmerman, M., Ruggero, C., Li, K., MacNamara, A., Weinberg, A., ... & Kotov, R. (2017). What do clinicians treat: Diagnoses or symptoms? The incremental validity of a symptom-based, dimensional characterization of emotional disorders in predicting medication prescription patterns. *Comprehensive Psychiatry, 79,* 80-88.

Wiggins, J. L., Mitchell, C., Hyde, L. W., & Monk, C. S. (2015). Identifying early pathways of risk and resilience: The codevelopment of internalizing and externalizing symptoms and the role of harsh parenting. *Development and Psychopathology, 27,* 1295-1312.

Wright, A. G., Hopwood, C. J., Skodol, A. E., & Morey, L. C. (2016). Longitudinal validation of general and specific structural features of personality pathology. *Journal of Abnormal Psychology, 125,* 1120-1134.

Zald, D. H., & Lahey, B. B. (2017). Implications of the hierarchical structure of psychopathology

for psychiatric neuroimaging. *Biological Psychiatry*, 2, 310-317.

Figure Captions

Figure 1. Working Hierarchical Taxonomy of Psychopathology (HiTOP) consortium model. Constructs higher in the figure are broader and more general, whereas constructs lower in the figure are narrower and more specific. Dashed lines denote provisional elements requiring further study. At the lowest level of the hierarchy (i.e., traits and symptom components), for heuristic purposes, conceptually related signs and symptoms (e.g., Phobia) are indicated in bold, with specific manifestations indicated in parentheses.

Figure 2. Conceptual diagrams of three possible HiTOP research designs. (A) Comparing the predictive validity across HiTOP levels. (B) Comparing predictive validity within a HiTOP level. (C) Comparing the predictive validity of categorical diagnoses to HiTOP dimensions. MDD = major depressive disorder; PDD = persistent depressive disorder; OSDD = other specified depressive disorder; BPD I = bipolar I disorder; BPD II = bipolar II disorder.

Figure 3. Heuristic model of the internalizing domain in relation to autonomic reactivity to a laboratory challenge. Paths A through C represent regressions of the outcome on dimensions at different levels of the hierarchical model. See main text for full details.

Figure 1

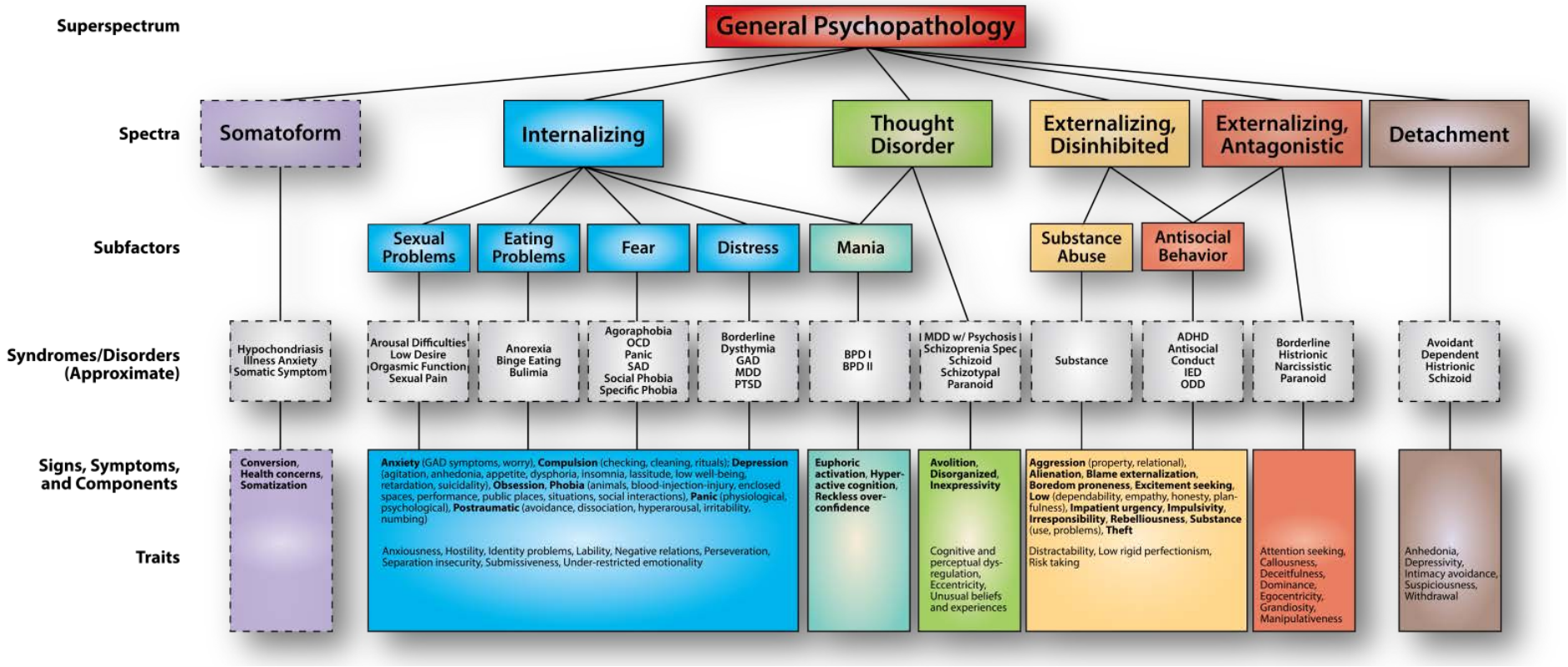

Superspectrum
General Psychopathology
Spectra
Somatoform
Internalizing
Thought Disorder
Externalizing, Disinhibited
Externalizing, Antagonistic
Detachment
Subfactors
Sexual Problems
Eating Problems
Fear
Distress
Mania
Substance Abuse
Antisocial Behavior
Syndromes/Disorders (Approximate)
Hypochondriasis Illness Anxiety Somatic Symptom
Arousal Difficulties Low Desire Orgasmic Function Sexual Pain
Anorexia Binge Eating Bulimia
Agoraphobia OCD Panic SAD Social Phobia Specific Phobia
Borderline Dysthymia GAD MDD PTSD
BPD I BPD II
MDD w/ Psychosis Schizoprenia Spec Schizoid Schizotypal Paranoid
Substance
ADHD Antisocial Conduct IED ODD
Borderline Histrionic Narcissistic Paranoid
Avoidant Dependent Histrionic Schizoid
Signs, Symptoms, and Components
Conversion, Health concerns, Somatization
Anxiety (GAD symptoms, worry), Compulsion (checking, cleaning, rituals); Depression (agitation, anhedonia, appetite, dysphoria, insomnia, lassitude, low well-being, retardation, suicidality), Obsession, Phobia (animals, blood-injection-injury, enclosed spaces, performance, public places, situations, social interactions), Panic (physiological, psychological), Postraumatic (avoidance, dissociation, hyperarousal, irritability, numbing)
Euphoric activation, Hyper-active cognition, Reckless over-confidence
Avolition, Disorganized, Inexpressivity
Aggression (property, relational), Alienation, Blame externalization, Boredom proneness, Excitement seeking, Low (dependability, empathy, honesty, plan-fulness), Impatient urgency, Impulsivity, Irresponsibility, Rebelliousness, Substance (use, problems), Theft
Traits
Anxiousness, Hostility, Identity problems, Lability, Negative relations, Perseveration, Separation insecurity, Submissiveness, Under-restricted emotionality
Cognitive and perceptual dys-regulation, Eccentricity, Unusual beliefs and experiences
Distractability, Low rigid perfectionism, Risk taking
Attention seeking, Callousness, Deceitfulness, Dominance, Egocentricity, Grandiosity, Manipulativeness
Anhedonia, Depressivity, Intimacy avoidance, Suspiciousness, Withdrawal

Figure 2

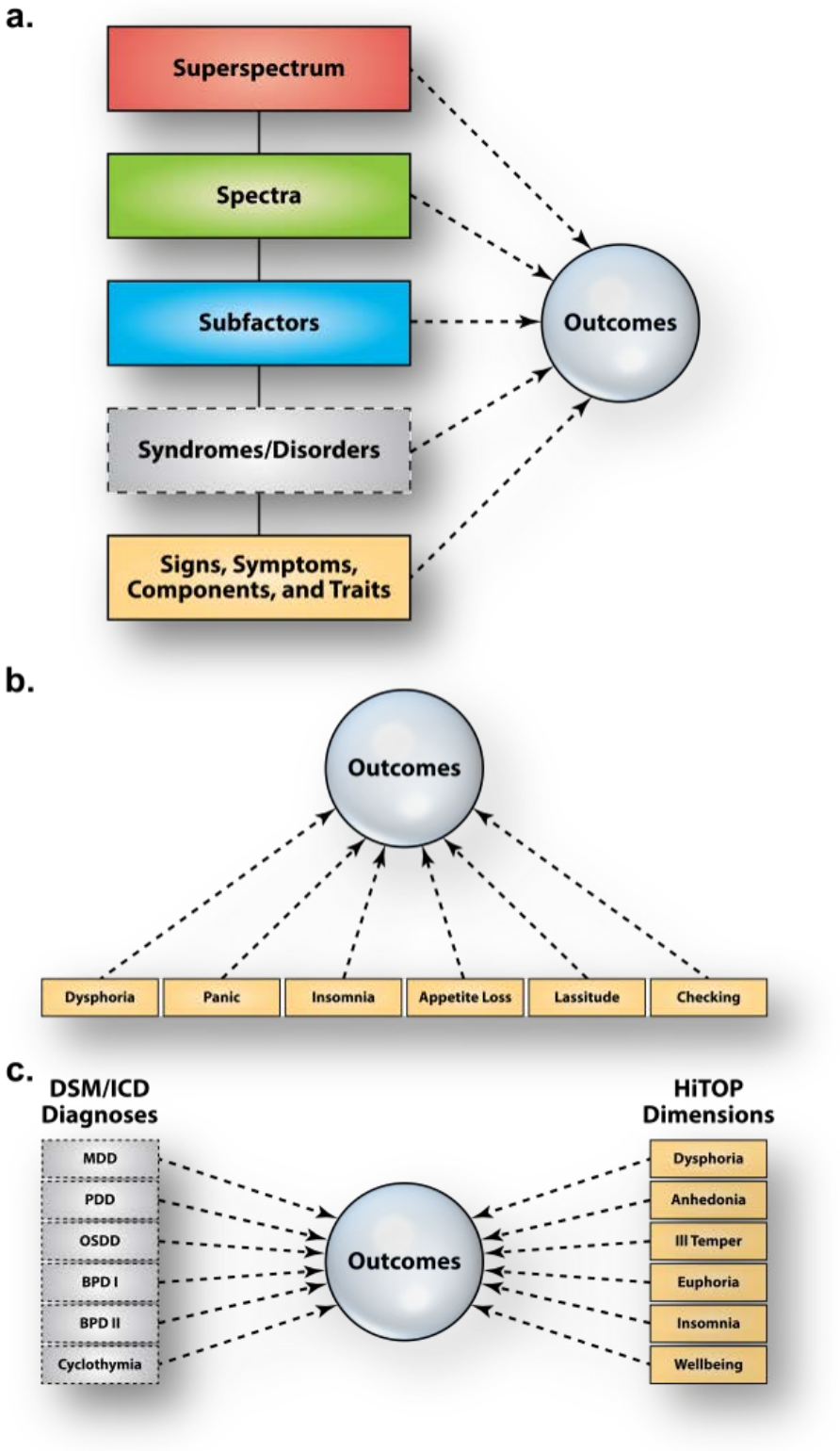
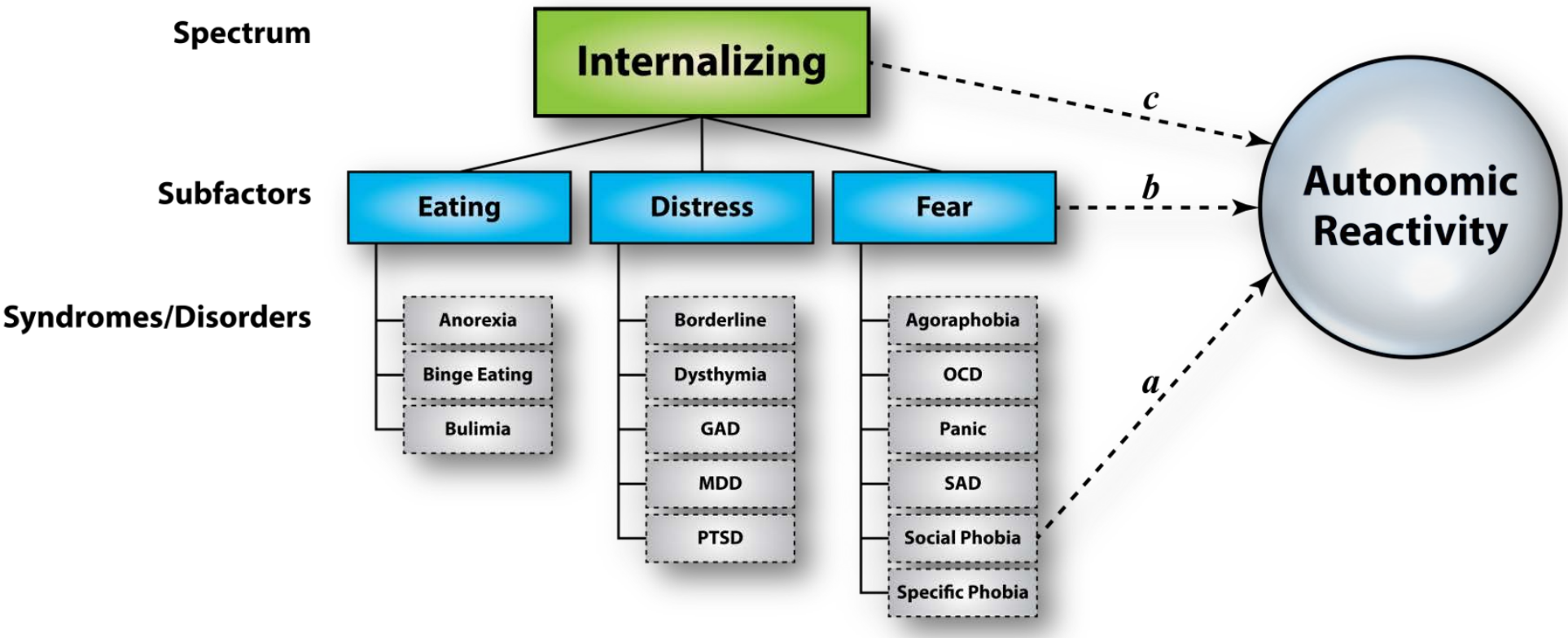

a.
Superspectrum
Spectra
Subfactors
Syndromes/Disorders
Signs, Symptoms, Components, and Traits
Outcomes
b.
Outcomes
Dysphoria
Panic
Insomnia
Appetite Loss
Lassitude
Checking
c.
DSM/ICD Diagnoses
MDD
PDD
OSDD
BPD I
BPD II
Cyclothymia
Outcomes
HiTOP Dimensions
Dysphoria
Anhedonia
Ill Temper
Euphoria
Insomnia
Wellbeing

Figure 3


Spectrum
Subfactors
Syndromes/Disorders
Internalizing
Eating
Distress
Fear
Anorexia
Binge Eating
Bulimia
Borderline
Dysthymia
GAD
MDD
PTSD
Agoraphobia
OCD
Panic
SAD
Social Phobia
Specific Phobia
c
b
a
Autonomic Reactivity