Abstract: 248 words
Text: 4,555 words
Figures: 5
Online Supplement: 2

The Hierarchical Taxonomy of Psychopathology (HiTOP) in Psychiatric Practice and Research

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This work was supported by the National Institute of Mental Health (LJS & RK, grant number R01MH122537, and KGJ, grant number R21MH123908).

Abstract

The Hierarchical Taxonomy of Psychopathology (HiTOP) has emerged out of the quantitative approach to psychiatric nosology. This approach identifies psychopathology constructs based on patterns of co-variation among signs and symptoms. The initial HiTOP model, which was published in 2017, is based on a large literature that spans decades of research. HiTOP is a living model that undergoes revision as new data become available. Here we discuss advantages and practical considerations of using this system in psychiatric practice and research. We especially highlight limitations of HiTOP and ongoing efforts to address them. We describe differences and similarities between HiTOP and existing diagnostic systems. Next, we review the types of evidence that informed development of HiTOP, including populations in which it has been studied and data on its validity. The paper also describes how HiTOP can facilitate research on genetic and environmental causes of psychopathology as well as the search for neurobiologic mechanisms and novel treatments. Furthermore, we consider implications for public health programs and prevention of mental disorders. We also review data on clinical utility and illustrate clinical application of HiTOP. Importantly, the model is based on measures and practices that are already used widely in clinical settings. HiTOP offers a way to organize and formalize these techniques. This model already can contribute to progress in psychiatry and complement traditional nosologies. Moreover, HiTOP seeks to facilitate research on linkages between phenotypes and biological processes, which may enable construction of a system that encompasses both biomarkers and precise clinical description.

The Hierarchical Taxonomy of Psychopathology (HiTOP) in Psychiatric Practice and Research

1. What is the Hierarchical Taxonomy of Psychopathology (HiTOP)?

The HiTOP consortium (http://medicine.stonybrookmedicine.edu/HITOP) is an effort to articulate a fully empirical classification of psychopathology, defined by findings of nosologic research. Its main motivation is to make psychiatric nosology more useful for clinicians and scientists. The consortium currently has 170 members, both psychologists and psychiatrists. The initial HiTOP model was published in 2017 (Kotov et al., 2017) and has been elaborated in 23 subsequent publications. The present paper reviews this research, new initiatives, and their implications for psychiatric practice and research.

HiTOP follows the quantitative approach to nosology that seeks to identify natural constellations of signs and symptoms. Over 90 years, this approach produced influential models and widely used measures, including the Child Behavior Checklist (CBCL) and Positive and Negative Syndrome Scale (PANSS) (Achenbach 1966; Kay et al., 1987; Lorr et al. 1963; Moore 1930). Similar techniques elucidated classifications of affect, personality, and cognitive abilities (Costa & McCrae 2008; McGrew 2009; Watson, 2000). In its publications, the HiTOP consortium integrated evidence from 261 studies of psychopathology structures and 293 studies of their validity and utility (Kotov et al., 2021). It considered all relevant evidence, including studies that directly measured HiTOP constructs, modeled constructs statistically, or identified common patterns across conditions comprising constructs (e.g., problems that define the internalizing spectrum). Construct names differed across studies and were synchronized to a common nomenclature.

Figure 1 shows the resulting model. Highly correlated specific dimensions are grouped into more general dimensions. Signs, symptoms, and maladaptive behaviors are combined into homogeneous components or traits (e.g., insomnia); those form broader dimensional syndromes (e.g., vegetative depression); closely-related syndromes are combined into subfactors (e.g.,

distress); larger groups of syndromes form spectra (e.g., internalizing); and those are combined into superspectra (e.g., p-factor). Specifically, the p-factor represents features common across all of psychopathology, whereas lower-order dimensions capture unique features. Scientists and clinicians can focus on the level of hierarchy needed for a given question (e.g., p-factor to identify high utilizers of care, specific components to test potential new medication).

The main outstanding structural questions for HiTOP are determining placement of provisional constructs, explicating empirical syndromes, and adding spectra to expand psychopathology coverage. Studies are ongoing to address these gaps.

2. **How is HiTOP different from DSM-5 and ICD-11?**

HiTOP is similar to traditional diagnostic manuals in its atheoretical, descriptive approach and focus on clinical features—signs and symptoms. HiTOP differs from DSM-5 and ICD-11 in conceptualizing psychopathology as extremes of normal psychological functions, such as affective processes, personality traits, and cognitive abilities. Traditional manuals mirror classifications of infectious diseases, which are naturally discrete conditions; whereas HiTOP parallels internal medicine, where many disorders are recognized as continuous with normal functioning (Agarwal et al., 2012; American Diabetes Association, 2010; Whelton et al., 2018). Existing research consistently supports the continuity between normality and psychopathology (Haslam et al. 2020; Krueger et al. 2018). Consequently, HiTOP constructs are dimensional.

Figure 2 illustrates the mismatch between categorical diagnoses and the nature of psychopathology, which results in four problems. First, extensive evidence indicates that traditional diagnoses have modest interrater reliability and shift over time (Bromet et al. 2011; Regier et al. 2013). This problem is unavoidable because diagnostic boundaries are arbitrary, and the modal case is just above the threshold. Second, even more people fall right below the threshold and are not captured by this system despite substantial symptom burden (Linscott & Van Os, 2013; Verheul & Widiger, 2004). Third, most patients have multiple disorders (Caspi et al. 2020; Kessler et al. 2005). Correlations among psychopathology dimensions result in high

comorbidity among disorders and proliferation of boundary diagnoses (e.g., schizoaffective disorder). Fourth, many diagnoses are heterogeneous and contain multiple psychopathology dimensions (Galatzer-Levy & Bryant 2013; Hasler et al. 2004).

HiTOP addresses each problem. Dimensional description substantially improves reliability (Markon et al. 2011; Narrow et al. 2013). Every patient is characterized by a profile on HiTOP dimensions. Comorbidity is represented by spectra and subfactors. Heterogeneity is reduced by identifying empirically coherent dimensions. Traditional manuals already include some dimensions, and HiTOP fully embraces this movement. Conversely, traditional diagnoses hold an advantage in considering illness course, while HiTOP works toward incorporating course characteristics.

3. **Is HiTOP applicable to diverse populations?**

Many quantitative studies focused on people aged 15 to 65 who live in Western societies (Kotov et al., 2021). HiTOP also reflects a growing literature on other populations. Internalizing and externalizing spectra were first identified in children (Achenbach, 1966) and have been extensively studied in youth. These spectra are observed in children as young as two years and are consistent across development (McElroy et al., 2018; Murray et al., 2016; Olino et al., 2018; Sterba et al., 2010). Research on elders is more limited, but suggests that the HiTOP structure remains consistent with age, including people as old as 102 (Eaton et al., 2011; Hoertel et al., 2015; Sunderland et al., 2013). However, existing studies have been limited to higher-order dimensions.

In the United States, HiTOP spectra were found to generalize across gender, race/ethnicity, and sexual orientation (Eaton, 2014, 2020; Eaton et al., 2012, 2013; He & Li, 2021; Suzuki et al., 2019). Cross-cultural studies reported consistent psychopathology structures across 24 Western and 25 non-Western societies (Ivanova et al., 2007, 2015, 2019; Krueger et al., 2003). Large-scale studies are needed to fully test HiTOP across sociodemographic groups and cultures. The consortium seeks collaborations with local experts to complete them.

4. **Is HiTOP validated?**

In traditional manuals, a new disorder is expected to undergo validation showing that it improves understanding of etiology, pathophysiology, prognosis, or treatment response (Andrews et al., 2009; Robins & Guze, 1970). However, the process for constructing diagnostic criteria is not specified. Consequently, a diagnosis may have external validity but lack internal coherence. For example, if disorder criteria were selected because each indicates poor prognosis among inpatients, the resulting diagnosis is likely to be quite heterogeneous although useful for prognostication. In contrast, HiTOP starts by analyzing relations among signs and symptoms to identify coherent and distinct constructs, which are then validated to determine their utility. HiTOP systematizes the process of nosologic discovery and retains external validation. Evidence of both internal coherence and external validity guides ongoing revision of HiTOP, which is intended as a living model (Kotov et al., 2021).

Several reviews related HiTOP dimensions to validators. They generally found that spectra reflect genetics, environmental risk factors, childhood antecedents, neurobiological alterations, biomarkers, and treatment response common across their components (Kotov et al., 2020; Krueger et al., 2021; Lynch et al., 2021; Watson et al., 2021). In other words, conditions placed on the same HiTOP spectrum had similar validator profiles.

Moreover, HiTOP dimensions can improve prognostication over traditional diagnoses. Dimensions were found to predict clinical improvement, treatment needs, and community functioning—in the short-term and long-term—across various outpatient and inpatient populations (Cervin et al., 2021; Conway et al., 2021; Forbush et al., 2018; Martin et al., 2021; Morey et al., 2012). HiTOP also outperformed traditional diagnoses in predicting important life outcomes, such as all-cause mortality (Kim et al., 2021).

HiTOP also informs treatment selection. Several pharmacotherapies and psychotherapies were found to be efficacious across disorders linked to a given spectrum, suggesting that these interventions treat the spectrum. For example, selective serotonin reuptake inhibitors are

efficacious for numerous internalizing conditions (Cipriani et al., 2018; Gosmann et al. 2021), and motivational interviewing psychotherapy reduces various disinhibited behaviors (Lundahl et al., 2010). Likewise, effective treatments have been identified for many narrower dimensions, such as exposure therapy for the fear subfactor (Craske et al., 2014), behavioral activation for anhedonia (Forbes, 2020), and sleep restriction therapy for insomnia (Edinger et al., 2021).

Ten studies directly compared the power of traditional diagnoses and HiTOP to account for validators concurrently and years later (Figure 3 and Supplemental Table 1). HiTOP was superior in 26 of 28 comparisons, with a mean 25.2% variance explained vs. 10.7% for diagnoses. These data are encouraging, but validation of HiTOP is only beginning.

5. **How can HiTOP be used clinically?**

In HiTOP, the diagnosis is the patient's profile on psychopathology dimensions (Ruggero et al., 2019). In the profile, spectra and subfactors describe the main difficulties the patient experiences, whereas components and traits detail specific issues. Symptom components capture current problems, whereas traits indicate their chronicity (e.g., high dysphoria component coupled with normal-range trait depressiveness suggest an acute problem with good prognosis). Impaired functioning in society is assessed separately from psychological dysfunction, recognizing that not all patients with significant psychopathology are disabled by it, similar to the distinction that ICD-11 makes between disorder and disability (Clark et al., 2017).

The HiTOP approach has four implications for treatment planning. First, clinicians can consider treatment targets both at higher levels, where treatment can affect multiple problems simultaneously (Mullins-Sweatt et al., 2020), and at lower levels, when a specific behavior is particularly significant (e.g., suicidality, opioid abuse) or requires a specialized intervention (e.g., hypnotic drug for insomnia). Second, dimensional case formulation highlights provision of care along the continuum of severity. Clinical actions are usually dichotomous and different actions are appropriate for different levels of severity. HiTOP allows multiple ranges to be specified on a dimension, each indicating a particular action (e.g., low range for prevention, higher for

outpatient treatment), whereas traditional diagnosis provides only one threshold. Third, traits provide valuable prognostic information and can substantially outperform traditional lifetime diagnoses in forecasting outcomes (Waszczuk et al., 2021). Fourth, comprehensive assessment identifies patient's strengths (i.e., traits in adaptive range) and weaknesses beyond the current treatment target. For instance, elevated mistrust and irresponsibility traits may guide providers to modify the format of depression treatment to pre-empt potential non-adherence (Bagby et al., 2016).

These strategies are not new. Physicians commonly consult other dimensional assessments, such as neuropsychological and intelligence testing (Harvey, 2012). Medical laboratory tests also provide continuous scores with significant elevations identified. HiTOP extends these practices to behavioral profiling. Importantly, a HiTOP profile is only one element of a psychiatric evaluation. Clinicians integrate the profile with other data (e.g., medical comorbidities, stressors, treatment history) to develop case formulation. HiTOP contributes a quantified, detailed, and systematic description of psychopathology to this process.

6. **How to evaluate patients using HiTOP?**

The consortium is developing self-report and interview measures to assess constructs included in the model and add missing constructs. This project is a collaboration of 40 psychometrics experts. It follows established procedures for the construction of distinct, reliable, and efficient scales (Clark & Watson, 2019; Loevinger, 1957). Study protocol and interim results have been published (Simms et al., 2022), and the HiTOP self-report inventory will be available to researchers in 2022. Next, the consortium will validate the measure—collecting normative, external validity, and clinical utility data—and make it available to clinicians. The consortium is also constructing an interview version, brief screeners that capture broad spectra, and indices for detection of invalid reporting. All measures will be free and open-source, with both digital and paper-and-pencil forms.

While these measures are in development, the consortium recommends HiTOP-consistent self-report, informant-report, and interviews tools that already are used clinically (see https://hitop.unt.edu/clinical-tools/hitop-friendly-measures). A subset of these scales that captures the majority of HiTOP dimensions was assembled into a digital tool, the HiTOP Digital Assessment and Tracker (HiTOP-DAT). It assesses symptoms and traits within each spectrum as well as functional impairment. The HiTOP-DAT is used for intake in a growing number of clinics. Patients complete it securely online from home or waiting room. Responses are scored automatically, referenced to norms, and the report is immediately emailed to the clinician. The report can be easily uploaded to an electronic health record, similar to laboratory test results. Figures 4 and 5 illustrate clinical use of the HiTOP-DAT on a case example.

The consortium published a manual on clinical application of the HiTOP-DAT (https://osf.io/8hngd/). It includes description of the HiTOP-DAT and guidelines for using it in diagnosis and treatment planning. Reimbursement for services relies on ICD-10-CM codes, so the manual includes a crosswalk to translate HiTOP elevations into these codes (e.g., high eating pathology subfactor into F50.9 Eating disorder, checking component into F42.9 Obsessive-compulsive disorder). Other training materials are freely available, such as a HiTOP-DAT workshop (https://hitop.unt.edu/introduction).

The HiTOP-DAT is compatible with other applications. A screener can be used to identify elevated spectra and focus assessment of lower-level dimensions within these domains, thus reducing patient burden. A monitoring version of HiTOP-DAT can be used to track treatment systematically. It includes scales relevant to the patient and is sent on a desired schedule. The screener or full inventory can be distributed to populations (e.g., students in a school, patients in a primary care clinic), allowing psychopathology detection and prevention on a large scale.

Currently, the HiTOP-DAT uses interpretive ranges specified in reference to norms (e.g., marked elevation is a score >97.5th percentile in the general population), similar to many laboratory or neuropsychological tests (Ruggero et al., 2019). Further research is needed to

specify ranges for particular clinical actions, following examples of internal medicine (e.g., hypertension stages; Whelton et al., 2018) and clinical staging (Shah et al., 2020).

7. **What is the clinical utility of HiTOP?**

Traditional diagnoses show limited clinical utility, evident in practitioners frequently making diagnoses without applying DSM criteria (First & Westen, 2007) and in extensive off-label prescribing (Taylor, 2016). Clinicians report that diagnosis provides little guidance in treatment selection and prognostication, and is used primarily for billing, training, and communication among professionals (First et al., 2018). Psychiatrists often rely on presenting symptoms rather than diagnoses to plan treatment (Waszczuk, Zimmerman et al., 2017). HiTOP can formalize this practice, offering a rigorous framework for dimensional, symptom-oriented, and personality-informed case formulation.

Many studies have surveyed clinicians about the utility of HiTOP dimensions versus traditional diagnoses for personality pathology (Bornstein & Natoli, 2019; Milinkovic & Tiliopoulos, 2020; Widiger, 2019). Results clearly favor HiTOP, especially in treatment formulation and communication with patients. This pattern was observed for both psychiatrists and other clinicians, contradicting a common assumption that psychiatrists prefer categories (Morey et al., 2014). Similar findings are emerging for other mental disorders (Mościcki et al., 2013). In a pilot survey, clinicians trained in HiTOP rated it as equivalent or superior to DSM-5 for building therapeutic alliance, prognostication, treatment selection, education of consumers, documentation, and communication with professionals (Supplemental Table 2). Further data on clinical utility are being collected in HiTOP-DAT Field Trials, ongoing at nine clinical sites.

HiTOP can enrich teaching of psychiatric assessment and diagnosis. Originally, phenomenology of mental illness was central to psychiatric training, despite the diverging diagnostic perspectives of Kraepelin, Bleuler, Meyer, Jaspers and others. DSM-III brought consistency to psychiatric diagnosis, but in some programs residents' knowledge of psychopathology was limited to DSM criteria and they no longer learned careful psychiatric

evaluation (Andreasen, 2007). Psychometric models of personality generally receive insufficient attention in both biologically- and psychodynamically-oriented programs. Filling these gaps, HiTOP organically organizes trainees' understanding of psychopathology along major spectra. It adds phenomenological knowledge from trait psychology (e.g., maladaptive traits) and descriptive psychopathology. Hence, HiTOP naturally fits the curriculum of the first year of residency.

8. **Can HiTOP guide prevention and public health programs?**

The prevalence of mental disorders has not decreased in several decades (James et al., 2018). This underscores the difficulty of treating psychopathology once it has developed and the importance of primary prevention (McDaid et al., 2019). The most cost-effective preventive interventions target high-risk groups rather than the entire population (Arango et al., 2018). However, diagnostic manuals were designed to describe full-fledged disorders and provide little guidance for identifying individuals with nascent psychopathology that has not yet reached the clinical threshold.

HiTOP thoroughly characterizes subthreshold psychopathology, providing a graded and multidimensional picture of vulnerabilities. Moreover, repeated HiTOP assessment (e.g., annual screening) can identify individuals with escalating risk. This assessment can augment traditional risk factors (e.g., family history, trauma exposure). The resulting description may offer a valuable guide for prevention (Forbes et al., 2019). Clinical staging models also aim to inform prevention (Frank et al., 2015; Shah et al., 2020). They seek to describe illness course across stages and identify optimal treatments for each stage. HiTOP is compatible with staging models by offering dimensional constructs that can be categorized into stages and companion measures that can trace stage progression over time.

Public health programs also need to detect full-fledged psychopathology in the general population, as only some people with mental health needs seek services (Regier et al., 1993; Wang et al., 2007). However, diagnostic manuals were designed for psychiatric settings.

Furthermore, traditional diagnostic assessments require a clinical interview, which limits their scalability. HiTOP can be accurately assessed either by interview or self-report (Simms et al., 2022). Self-reports administered online can screen large populations to facilitate early detection and intervention.

Public health statistics usually focus on numbers of cases, which overlooks both subthreshold symptoms in non-cases and differences in severity among cases. This likely underestimates the impact of psychopathology (Lahey, 2009; Ruscio, 2019). Likewise, efficacy of interventions is often expressed as the number needed to treat to achieve a categorical outcome (e.g., abstinence from alcohol), which does not capture graded improvement (e.g., reduced consumption). HiTOP allows calculation of the cumulative symptom burden or the cumulative treatment benefit across the full range of the target dimension. It also permits computation of traditional statistics (e.g., prevalence, incidence) using severity ranges as categories. These promising applications of HiTOP in public health management require rigorous testing.

9. **Can HiTOP advance understanding of etiology and pathophysiology?**

HiTOP offers good targets for genetic research, as ample evidence—both behavioral and molecular—indicates that the model is aligned with the genetic architecture of psychopathology (Waszczuk et al., 2020). First, genetic vulnerability to psychopathology is normally distributed and associated with the full range of the target phenotype, from healthy (e.g., minor distractibility) to clinical (e.g., attention-deficit/hyperactivity disorder) (Martin et al., 2018; Plomin et al., 2009), consistent with a dimensional nosology. Second, psychiatric phenotypes show high genetic overlap, with many genetic variants influencing multiple phenotypes (Lee et al., 2019; Martin et al., 2019). A hierarchical approach helps to understand this pleiotropy as risk variants that contribute to higher-order dimensions (Grotzinger et al., 2019; Levey et al., 2021). Third, genetic similarities among disorders largely parallel their placement in HiTOP spectra

(Kotov et al., 2020; Krueger et al., 2021; Watson et al., 2021). Accordingly, HiTOP dimensions can be better phenotypes for genetic research than traditional diagnoses.

Specifically, genome-wide association studies (GWAS) of HiTOP dimensions can identify more genetic risk loci than studies of DSM-5 disorders due to improved reliability. This advantage already was observed in GWAS of the externalizing superspectrum (Linner et al., 2020). HiTOP also can help to explicate common and unique loci. The existing approach requires complex multivariate models. HiTOP simplifies this task by providing direct measurement of general and specific phenotypes. Moreover, GWAS with imprecise phenotyping tend to finds loci that predict many forms of psychopathology, whereas precise phenotyping improves specificity (Cai et al., 2020). Existing psychiatric polygenic risk scores (PRS) largely capture genetic vulnerability for psychopathology broadly rather than for a specific disorder (Waszczuk et al., 2021). GWAS of HiTOP constructs could produce more precise PRS.

HiTOP also can help to explicate the role of environmental factors in psychopathology. Exposures such as childhood maltreatment, peer victimization, discrimination, and family and romantic strains are implicated in numerous disorders. Studies consistently find that these factors influence spectra, with little additional effect on specific disorders (Conway et al., 2018, 2019; Forbes et al., 2020; Keyes et al., 2012; Rodriguez-Seijas et al., 2015; Vachon et al., 2015). HiTOP spectra can account for such environmental effects parsimoniously. Other exposures are hypothesized to elicit specific forms of psychopathology, such as peer rejection contributing to the development of social anxiety (Spence & Rapee, 2016), but have been difficult to test because of comorbidity. A hierarchical nosology can control for comorbidity to pinpoint specific effects of such exposures.

HiTOP can facilitate research on the neurobiology of mental disorders by providing more specific and reliable targets than traditional diagnoses (Latzman et al., 2020). HiTOP's higher-order dimensions capture neural abnormalities common across multiple disorders, and already have shown replicable links to biobehavioral systems (Michelini et al., 2021). We illustrate this with three findings. First, the p-factor is associated with reduced thickness across much of the

neocortex (Romer et al., 2019). Second, the internalizing spectrum is consistently linked to altered amygdala function and connectivity with the anterior cingulate cortex (Hur et al., 2019; Marusak et al., 2016). Third, the externalizing superspectrum is correlated with reductions in an electroencephalography signal indexing cognitive control (Venables et al., 2018). However, more work is needed to fully evaluate advantages of HiTOP for etiologic research. Moreover, HiTOP is focused on behavioral patterns and would miss abnormalities that manifest in various unrelated symptoms. This possibility needs to be examined in further research.

10. **How can HiTOP accelerate drug discovery?**

Animal models are critical to drug discovery, but poor alignment between these models and traditional diagnoses hinders treatment development (Hyman, 2007). It is more feasible to develop an animal model for a specific psychopathology dimension than a heterogeneous, categorical diagnosis (e.g., for social withdrawal rather than schizophrenia) (Donaldson & Hen, 2015). For example, a nonhuman primate model has been established for trait anxiousness (Kenwood & Kalin, 2021). This enabled explication of neurogenetic mechanisms that shape anxiousness (Fox et al., 2015; Kenwood & Kalin, 2021). The identified mechanisms are expected to translate in humans not only to anxiousness but potentially the fear subfactor that contains this trait in HiTOP. Likewise, the anhedonia dimension has been guiding cross-species translation. Rodent research has shown that κ-opioid receptor antagonists improve deficient reward processing (Pizzagalli et al., 2020). Accordingly, a randomized controlled trial (RCT) selected participants based on elevated anhedonia across diagnoses and found that κ-opioid antagonist improves both neural reward processing and anhedonia symptoms (Krystal et al., 2020).

In humans, HiTOP suggests two design changes in RCTs. First, typical studies focus on one disorder and exclude participants with significant comorbidity. This improves rigor when disorders have distinct etiologies, but in psychiatry, etiologic effects largely cut across diagnostic boundaries (see Section 9). Also, most patients in real-world practice have multiple

comorbidities, so this design results in unrepresentative samples, diminishing the utility of RCTs (Moberg & Humphreys, 2017; Wisniewski et al., 2009). For treatments that act on spectra, this approach is inefficient because RCTs are required for each individual disorder, instead of fewer studies targeting the overall spectrum. For treatments that act on specific dimensions, efficacy may be obscured in RCTs targeting a heterogeneous disorder. HiTOP recommends selecting the sample according to elevation on the dimension of interest (e.g., broad internalizing, narrow checking). To maximize generalizability, exclusion criteria can be limited to factors with established effects on etiology (e.g., dementia can produce checking behavior) or treatment response (e.g., advanced age can alter drug's pharmacokinetics).

Second, typical RCTs assess few outcomes and may miss unanticipated treatment benefits (Joyce et al., 2017). HiTOP-based RCTs would include a comprehensive psychopathology assessment. This does not have to increase power requirements, if trial registration specifies primary endpoints and other dimensions are considered exploratory. Moreover, analyses of treatment effects on trajectories offer more statistical power than analyses of dichotomous outcomes. A growing number of RCTs are using HiTOP to measure treatment outcomes (Aitken et al., 2021; Constantinou et al., 2019).

HiTOP spectra have shown utility in the development of novel psychotherapies. For instance, the "unified protocol" was developed specifically for treatment of the internalizing spectrum and proved to be efficacious in numerous studies (Barlow et al., 2017; Carlucci et al., 2021). Many other therapies are in development or undergoing evaluation (Dalgleish et al., 2020). HiTOP is starting to inform pharmacologic research. For example, proposed targets for drug development include transdiagnostic social withdrawal, anhedonia, and dimensions of addiction, such as craving and impulsivity (Kas et al., 2019; Krystal et al., 2020; Volkow, 2020).

Currently, psychiatric medications receive regulatory approval for a specific disorder. The U.S. Food and Drug Administration (FDA) has approved treatment indications for some symptom components, but in the context of a specific disorder, such as irritability in autism or suicidal ideation in major depressive disorder (Canady, 2020; Robb, 2010). A dialogue with

regulatory agencies is needed to establish transdiagnostic dimensions as acceptable targets for treatment indications.

11. **What are the limitations of HiTOP?**

The current model is the first version of HiTOP and has notable limitations. First, it is not yet comprehensive. Research is ongoing to integrate other forms of psychopathology (e.g., cognitive impairments), clarify provisional placements (e.g., mania), and explicate empirical syndromes. Second, HiTOP does not include etiology. This was a deliberate decision, given limited understanding of mental disorders' etiology and difficulties in linking patient's symptoms to specific causes, such as dysphoria to trauma or psychosis to substance use (Larsen & Pacella, 2016; Starzer et al., 2018). When the etiology of symptoms is clear, a description of contributing factors is an important complement to a HiTOP profile. Third, HiTOP does not include course features (e.g., age of onset, number of episodes, illness duration). Instead, it can incorporate features of trajectories (e.g., mean level, variability over time, symptom cascades, sensitivity to triggers and treatments). Electronic health records and mobile monitoring technologies make explication of trajectories more feasible (Wright & Woods 2020). Inclusion of trajectory features in HiTOP is an important future direction. Fourth, existing practice guidelines are disorder-based. This knowledge needs to be translated to HiTOP constructs, and development of HiTOP-based guidelines is progressing. Fifth, HiTOP-based assessment may be unnecessarily detailed and potentially infeasible in acute settings, where a singular problem requires rapid intervention. Traditional diagnoses or assessments limited to HiTOP spectra may be optimal for emergency or inpatient care. However, long-term management and preventive interventions can benefit from the full model.

Other research priorities include validation of understudied HiTOP constructs, tailoring the model to different sociodemographic groups and cultures where needed, and systematic application of HiTOP in treatment development. The consortium also is working to maximize the clinical utility of HiTOP diagnosis (e.g., gathering clinician feedback, developing ranges for

clinical actions) and construct tools for seamless implementation of HiTOP in clinics. Further explication of links between HiTOP dimensions and etiologic processes (genetic, developmental, environmental, and neurobiological) may enable construction of a new nosology that encompasses both specific etiologies and precise clinical descriptions. The resulting system would include biomarkers along with symptom profiles and trajectories. To accelerate progress toward these goals, the consortium seeks partnerships with organizations that fund and promote psychopathology research.

12. **Conclusions**

The consortium has made substantial progress in this short time, but its work is only beginning. HiTOP promises a more reliable and accurate description of psychopathology than traditional manuals, but much of existing knowledge is based on disorders. Hence, while the HiTOP knowledge base matures, it may be prudent to use both nosologies—especially dimensional measures accompanying DSM-5. These systems can complement each other, facilitated by the crosswalk between them (see Section 6). HiTOP is already used clinically, which is possible because the model is based on measures and practices accepted in clinical settings. HiTOP organizes and formalizes these established techniques, providing symptom-oriented and personality-informed case formulation.

A more valid and useful nosology would benefit everyone in psychiatry: scientists, clinicians, trainees, and patients. Hence, in addition to the research consortium, we organized the Clinical Network for practitioners interested in translation to care and the Trainee Network for residents and graduate students. We encourage everyone interested to join the effort (https://renaissance.stonybrookmedicine.edu/HITOP/GetInvolved).

Funding Statement: This work was supported by the National Institute of Mental Health (LJS & RK, grant number R01MH122537, and KGJ, grant number R21MH123908).

Conflicts of Interest: Author SEH is on the Scientific Advisory Boards of Janssen Pharmaceuticals and F-Prime Capital.

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Figure 1. Hierarchical Taxonomy of Psychopathology (HiTOP) model
Note. Dashed lines indicate dimensions included on a provisional basis, as data on them are limited. Qualifier "(low)" in front of a construct indicates negative relationship with the corresponding spectrum. DSM diagnoses are not included in HiTOP; rather symptoms and signs that constitute them are in the model; also, diagnoses have been used in research to identify HiTOP subfactors and spectra. HiTOP syndromes are empirically derived dimensions rather than DSM disorders. Abbreviations: ADHD = attention-deficit/hyperactivity disorder, DSM = Diagnostic and Statistical Manual of Mental Disorders, GAD = generalized anxiety disorder, IED = intermittent explosive disorder, MDD = major depressive disorder, OCD = obsessive–compulsive disorder, ODD = oppositional defiant disorder, SAD = separation anxiety disorder, PD = personality disorder, PTSD = posttraumatic stress disorder.

Figure 2. Simulated example of psychopathology distribution in psychiatric outpatients
Panel A shows distribution of psychiatric outpatients along dimensions of psychosis severity and depression severity. Scales range from no symptom (0 - 1), to subclinical (1 - 2), to clinical (>2). Density function of each symptom dimension is shown above or to the right of the scatterplot. No zones of rarity are observed. The two types of symptoms are correlated.
Panel B shows how traditional diagnostic manuals deal with the lack of natural boundaries and symptom correlation—they designate multiple mutually exclusive categories, represented here by color. Faded = no relevant diagnosis; blue = major depressive disorder; violet = major depressive disorder with psychotic features; purple = schizoaffective disorder; pink = schizotypal personality disorder; magenta = delusional disorder; red = schizophrenia.

Figure 3. Ability of a quantitative nosology and a traditional diagnostic system to explain or predict clinical status, functioning, services, and biomarkers across 10 studies. Bar graphs show joint explanatory power (R^2) of constructs from a given system.

Figure 4. Case vignette illustrating the clinical application of HiTOP

Figure 5. The HiTOP-DAT profile of the illustrative case
Raw scores are converted to t-scores, which have mean of 50 and standard deviation of 10 in the general population. Elevations are classified as mild (T-score: 61 – 65), moderate (66 – 70), or marked (>70). Scores can fall below 50, but this range is not shown for clarity.

Figure 1

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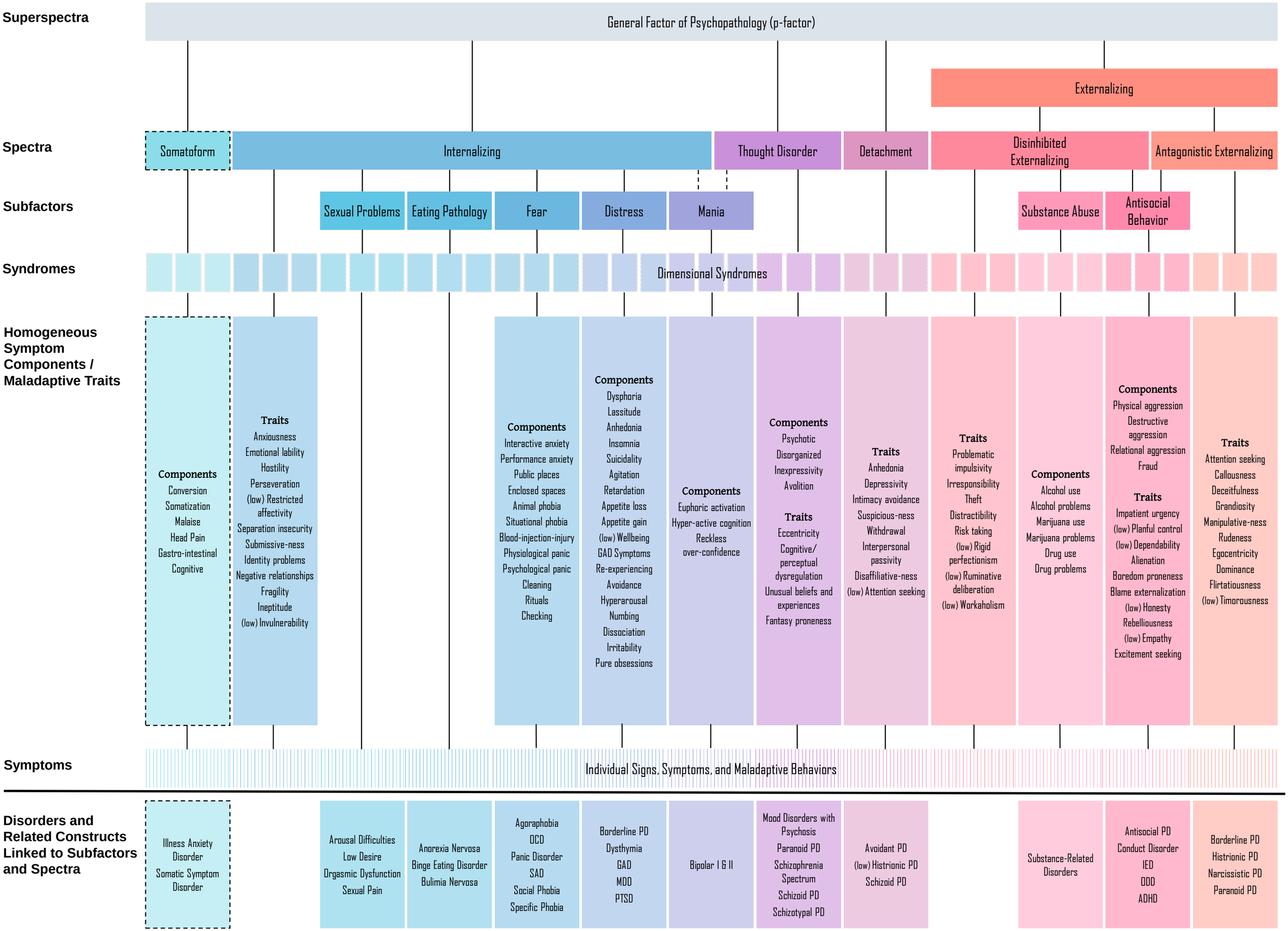

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Superspectra

General Factor of Psychopathology (p-factor)

Spectra

Somatoform

Internalizing

Thought Disorder

Detachment

Externalizing

Disinhibited Externalizing

Antagonistic Externalizing

Subfactors

Sexual Problems

Eating Pathology

Fear

Distress

Mania

Substance Abuse

Antisocial Behavior

Syndromes

Dimensional Syndromes

Homogeneous Symptom Components / Maladaptive Traits

Components
Conversion
Somatization
Malaise
Head Pain
Gastro-intestinal
Cognitive

Traits
Anxiousness
Emotional lability
Hostility
Perseveration
(low) Restricted affectivity
Separation insecurity
Submissive-ness
Identity problems
Negative relationships
Fragility
Ineptitude
(low) Invulnerability

Components
Interactive anxiety
Performance anxiety
Public places
Enclosed spaces
Animal phobia
Situational phobia
Blood-injection-injury
Physiological panic
Psychological panic
Cleaning
Rituals
Checking

Components
Dysphoria
Lassitude
Anhedonia
Insomnia
Suicidality
Agitation
Retardation
Appetite loss
Appetite gain
(low) Wellbeing
GAD Symptoms
Re-experiencing
Avoidance
Hyperarousal
Numbing
Dissociation
Irritability
Pure obsessions

Components
Euphoric activation
Hyper-active cognition
Reckless
over-confidence

Components
Psychotic
Disorganized
Inexpressivity
Avolition

Traits
Eccentricity
Cognitive/ perceptual dysregulation
Unusual beliefs and experiences
Fantasy proneness

Traits
Anhedonia
Depressivity
Intimacy avoidance
Suspicious-ness
Withdrawal
Interpersonal passivity
Disaffiliative-ness
(low) Attention seeking

Traits
Problematic impulsivity
Irresponsibility
Theft
Distractibility
Risk taking
(low) Rigid perfectionism
(low) Ruminative deliberation
(low) Workaholism

Components
Alcohol use
Alcohol problems
Marijuana use
Marijuana problems
Drug use
Drug problems

Components
Physical aggression
Destructive aggression
Relational aggression
Fraud

Traits
Impatient urgency
(low) Planful control
(low) Dependability
Alienation
Boredom proneness
Blame externalization
(low) Honesty
Rebelliousness
(low) Empathy
Excitement seeking

Traits
Attention seeking
Callousness
Deceitfulness
Grandiosity
Manipulative-ness
Rudeness
Egocentricity
Dominance
Flirtatiousness
(low) Timorousness

Symptoms

Individual Signs, Symptoms, and Maladaptive Behaviors

Disorders and Related Constructs Linked to Subfactors and Spectra

Illness Anxiety Disorder
Somatic Symptom Disorder

Arousal Difficulties
Low Desire
Orgasmic Dysfunction
Sexual Pain

Anorexia Nervosa
Binge Eating Disorder
Bulimia Nervosa

Agoraphobia
OCD
Panic Disorder
SAD
Social Phobia
Specific Phobia

Borderline PD
Dysthymia
GAD
MDD
PTSD

Bipolar I & II

Mood Disorders with Psychosis
Paranoid PD
Schizophrenia Spectrum
Schizoid PD
Schizotypal PD

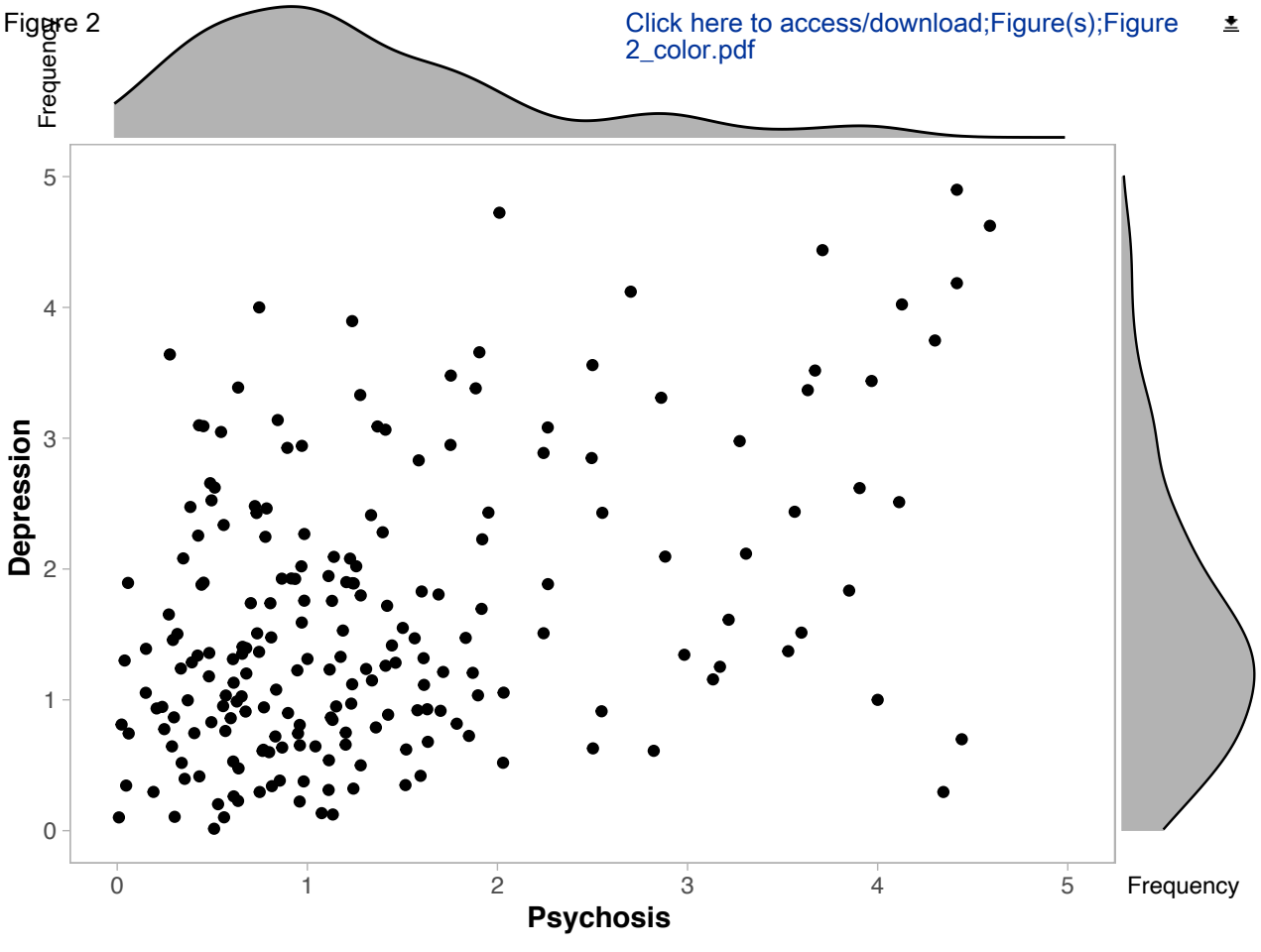
Avoidant PD
(low) Histrionic PD
Schizoid PD

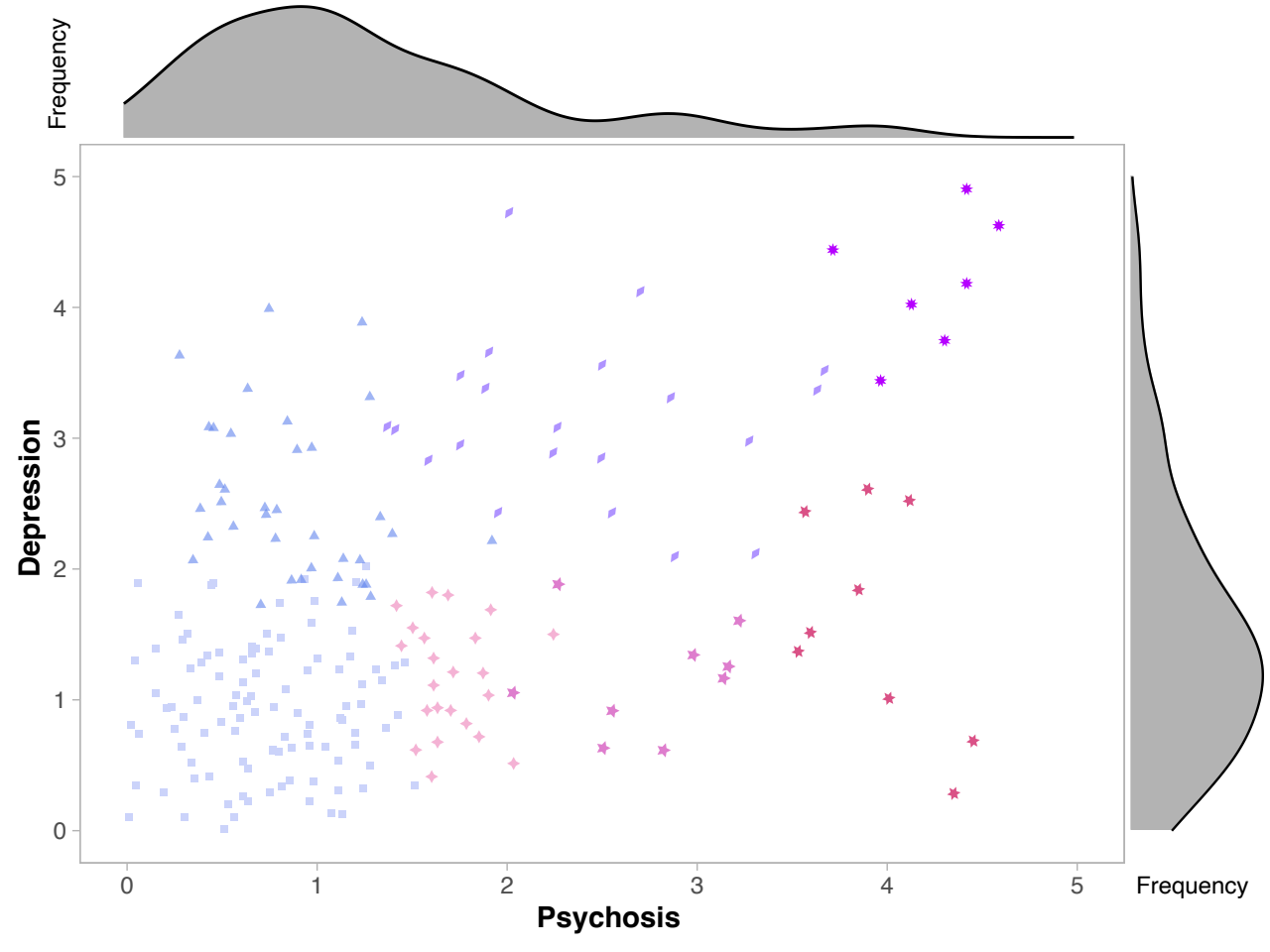
Substance-Related Disorders

Antisocial PD
Conduct Disorder
IED
ODD
ADHD

Borderline PD
Histrionic PD
Narcissistic PD
Paranoid PD

Figure 2




Frequency
Depression
0
1
2
3
4
5
Psychosis
Frequency

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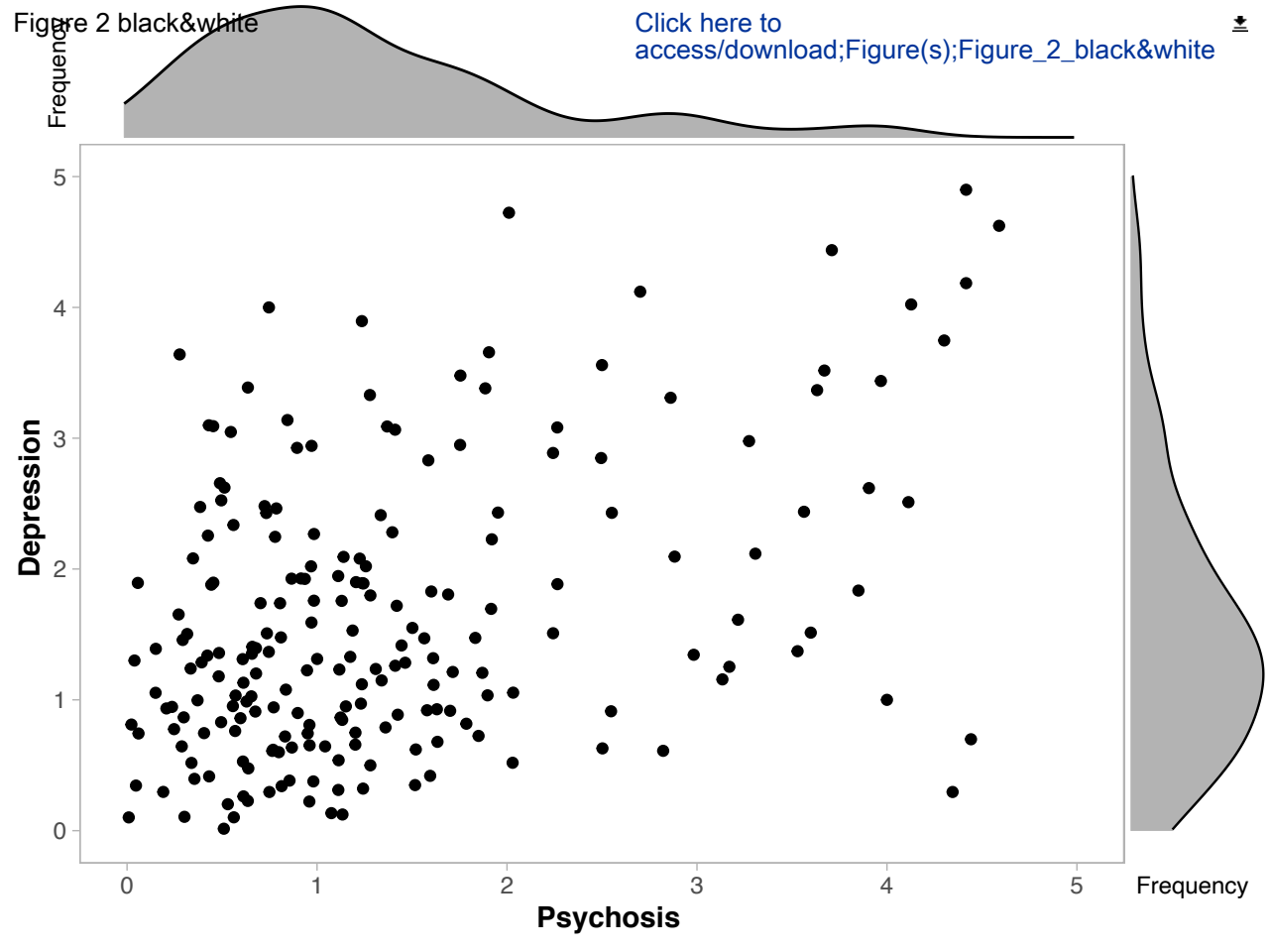

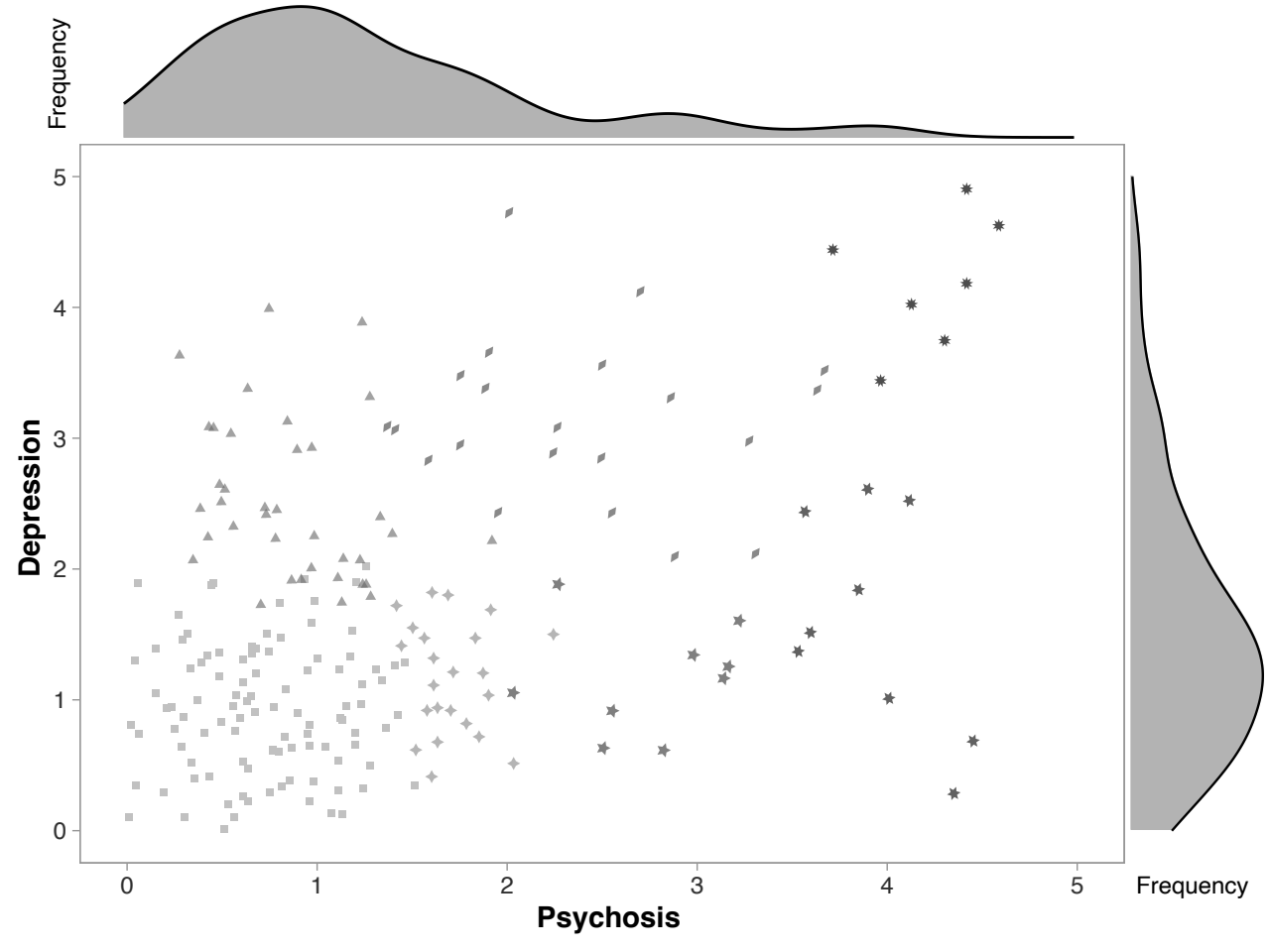
Frequency
Depression
Psychosis
Frequency
0
1
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3
4
5

Figure 3

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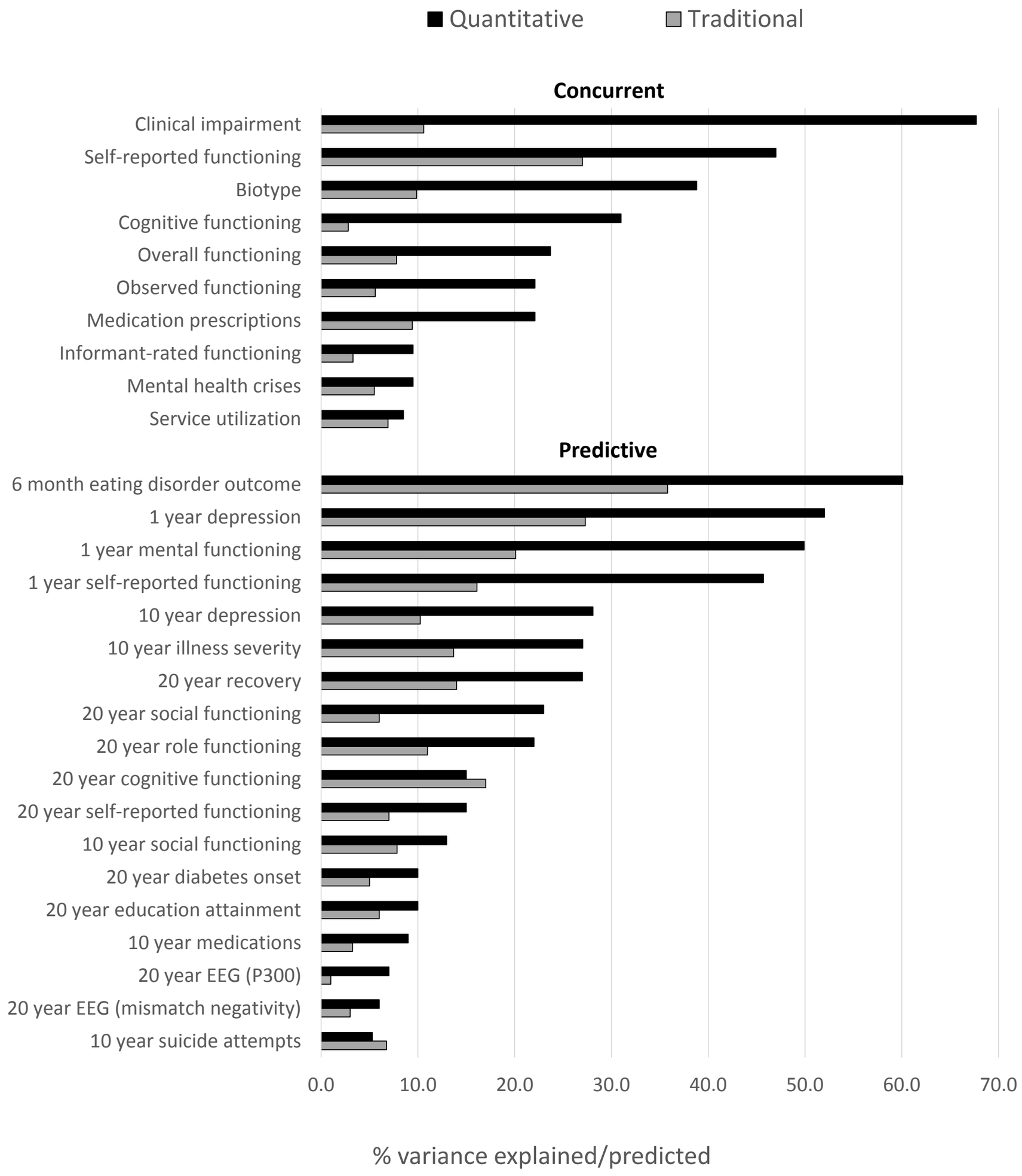

Figure 4. Case vignette illustrating the clinical application of HiTOP

Greg B. is a 29-year-old single male who works as a programmer. He contacted the outpatient psychiatry department seeking treatment for long-standing problems with anxiety. The precipitating event is that he recently terminated treatment with his previous psychiatrist because of perceived lack of improvement. Medical records show that he was previously diagnosed with generalized anxiety disorder, social anxiety disorder, panic disorder, posttraumatic stress disorder, major depressive disorder, and borderline personality disorder traits. He also has a diagnosis of alcohol use disorder in sustained remission. He received pharmacotherapy in the past, but has not had psychotherapy.

The department offers HiTOP-DAT as part of intake, which new patients complete on a secure online portal before the first visit. The psychiatrist has an option to send the patient a 5-minute screener that assess the six spectra, and then administer modules for elevated spectra only. However, given the complexity of this case, the psychiatrist elected to send the full HiTOP-DAT, a 45-minute inventory (Figure 5). It revealed moderate elevations on the internalizing spectrum. Among its lower-level traits and components, relatively high elevations were observed for suicidality and insomnia. Health anxiety was markedly elevated. Externalizing disinhibition was also elevated, driven by marked non-perseverance. Other spectra were within the normal range.

During intake, Greg was well-kempt and established rapport readily, but his mood was low and he often looked away or down. The psychiatrist interviewed Greg about problems indicated by HiTOP-DAT elevations. This revealed a history of non-suicidal self-injury and current passive suicidal ideation, but not intent, plan, or means. Greg has taken hypnotics on and off, but with only temporary relief from insomnia. Currently, he averages 5 hours of sleep a night and is often tired. He reported several visits to a primary care provider and specialists for abdominal pain without a clear resolution of his concerns. Records requested from these clinics revealed that none of Greg's concerns were confirmed by medical tests, and the resulting treatment was limited to non-steroidal anti-inflammatory drugs.

Under a DSM-5 conceptualization, a psychiatrist would consider treatment related to the six aforementioned disorders. A variety of pharmacotherapies and psychotherapies are indicated for these individual disorders (American Psychiatric Association, 2021; National Institute for Health and Care Excellence, 2021), but the best sequence of treatments for this complex case is uncertain. Moreover, no RCTs have been conducted for patients with this constellation of disorders, so the applicability of guidelines developed for individual disorders is unclear. Of note, elevations on health anxiety and non-perseverance were missed by a DSM-based evaluation.

The HiTOP conceptualization identified an elevated internalizing spectrum as the central problem. Selective serotonin reuptake inhibitors (SSRI) have established efficacy for this spectrum (Cipriani et al., 2018; Gosmann et al. 2021), so the psychiatrist prescribes an SSRI. Literature also indicates that across internalizing conditions, a combination of pharmacotherapy and psychotherapy is more efficacious than pharmacotherapy alone (Cuijpers et al., 2014). Accordingly, the psychiatrist discussed the benefits of combination treatment with Greg and

referred him to a psychologist who offers the unified protocol, a psychotherapy developed and validated for the internalizing spectrum (Carlucci et al., 2021). Insomnia is more elevated than the general internalizing spectrum, and hence is not expected to resolve fully even when the spectrum is effectively treated. The psychiatrist and patient decided to revisit insomnia in six month, and if it remains a problem, consider the addition of sleep restriction therapy—an efficacious treatment specific to insomnia (Edinger et al., 2021). Importantly, the antagonistic externalizing spectrum was in the normal range, and hence agreeableness (low antagonism) is a relative strength. This suggests that the working alliance likely will be successful, and Greg will accept treatment. However, elevated disinhibition signals a risk of non-adherence due to low persistence, and so the psychiatrist opted for monthly follow-up visits to monitor treatment adherence and any escalation of suicidality. To facilitate monitoring, the psychiatrist selected monthly tracking of internalizing symptoms (including suicidality) in HiTOP-DAT, which will automatically remind the patient to complete the assessment online before each visit. With Greg's permission, the psychiatrist contacted the primary care provider and offered help in reducing unnecessary use of medical services. They decided that the provider will consult the psychiatrist about Greg's future care as appropriate.

Note: This case is based on multiple patients to safeguard confidentiality.

Figure 5

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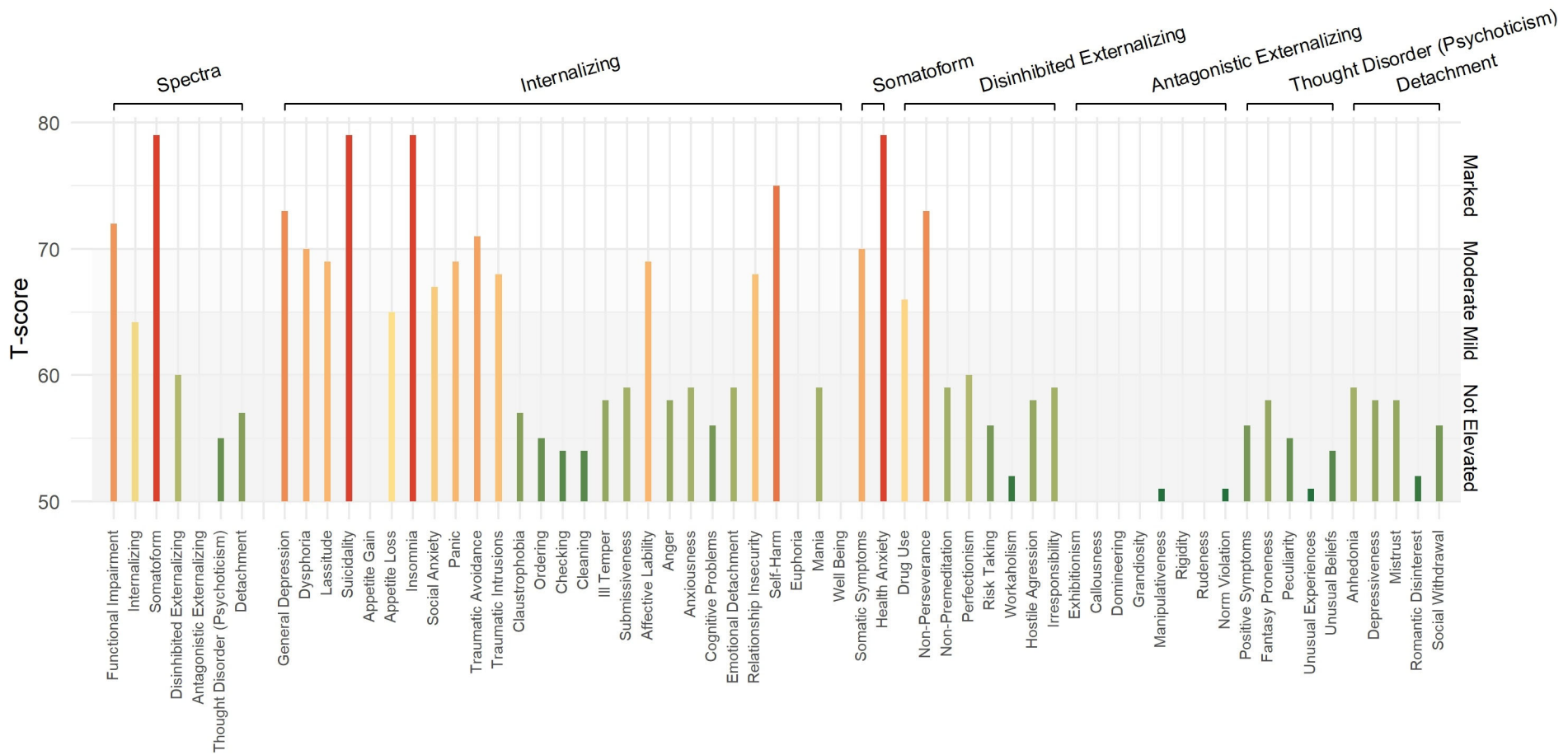

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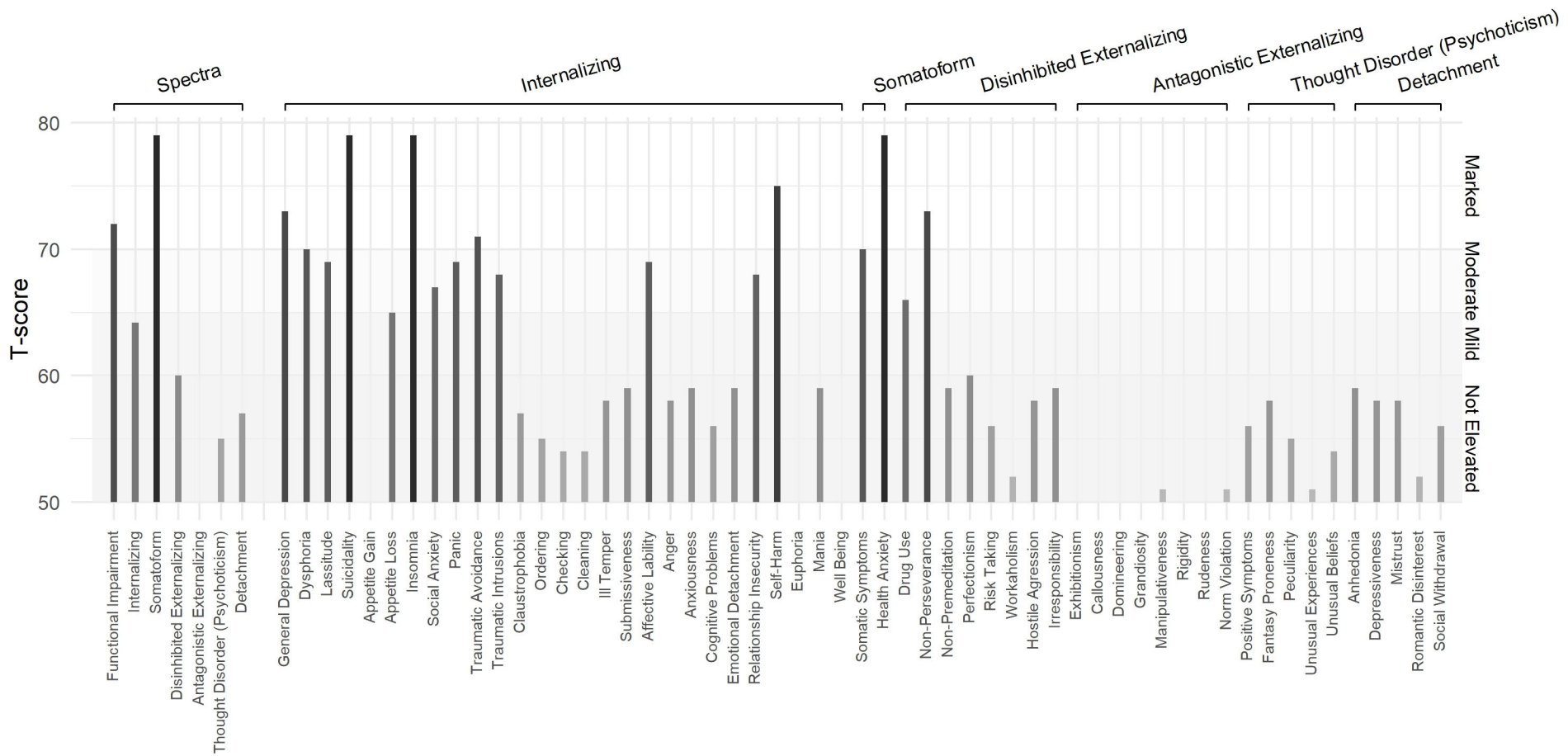

Supplemental Table 1. Details of studies included in Figure 3.

Citation	N	Sample	Outcome	Measure	Value of R^2		Transformation to R^2
					Traditional	Quantitative	
Forbush et al., 2017	207	Adults with eating disorders	Clinical impairment	Clinical Impairment Assessment	10.6	67.7	none
Waszczuk, Kotov et al., 2017	314	Adult psychiatric outpatients	Self-reported functioning	Sheehan Disability Scale	27.0	47.0	none
Reininghaus et al., 2019	933	Patients with psychotic disorders	Biotype	B-SNIP biotypes	9.9	38.8	Converted AUC to R2
Hanlon et al., 2019	150	Patients with psychotic disorders	Cognitive functioning	General cognitive ability (PCA on several tests)	2.8	31.0	none
Rosenman et al., 2003	982	Treatment seekers with lifetime psychotic disorder	Overall functioning	SOFAS	7.8	23.7	none
Hanlon et al., 2019	150	Patients with psychotic disorders	Observed functioning	UPSA	5.6	22.1	none
Waszczuk, Zimmerman et al., 2017	318	Adult psychiatric outpatients	Medication prescriptions	Mean AUC in predicting prescription of 7 classes of medications	9.4	22.1	Converted AUC to R2
Hanlon et al., 2019	150	Patients with psychotic disorders	Informant-rated functioning	SLOF	3.3	9.5	none
Rosenman et al., 2003	981	Treatment seekers with lifetime psychotic disorder	Mental health crises	In past year, involuntary hospitalizations, crisis teams, incidents of self-harm, & arrests	5.5	9.5	none
Rosenman et al., 2003	980	Treatment seekers with lifetime psychotic disorder	Service utilization	Voluntary hospitalizations, crisis teams, community services	6.9	8.5	none
Forbush et al., 2018	194	Adults with eating disorders	6 month eating disorder outcome	Weight and binging/compensatory behavior	35.8	60.1	none
Waszczuk et al., 2021	133	Trauma-exposed primary care adult patients	1 year depression	PHQ-9	27.3	52.0	none
Waszczuk et al., 2021	133	Trauma-exposed primary care adult patients	1 year mental functioning	Short-Form Health Survey	20.1	49.9	none

Forbush et al., 2018	109	Adults with eating disorders	1 year self-reported functioning	WHO-DAS total	16.1	45.7	none
Morey et al., 2012	668	Treatment seekers with personality disorder and/or depression	10 year depression	Personality Assessment Inventory depressice scale score at 10 year follow-up	10.2	28.1	Squared multiple R
Morey et al., 2012	668	Treatment seekers with personality disorder and/or depression	10 year illness severity	Global Assessment of Functioning at 10 year follow-up	13.7	27.0	Squared multiple R
Martin et al., 2021	316	First-admission psychosis	20 year recovery	Recovery	14.0	27.0	none
Martin et al., 2021	319	First-admission psychosis	20 year social functioning	Social functioning	6.0	23.0	none
Martin et al., 2021	318	First-admission psychosis	20 year role functioning	Role functioning	11.0	22.0	none
Martin et al., 2021	324	First-admission psychosis	20 year cognitive functioning	Cognition composite	17.0	15.0	none
Martin et al., 2021	320	First-admission psychosis	20 year self-reported functioning	WHO-DAS	7.0	15.0	none
Morey et al., 2012	668	Treatment seekers with personality disorder and/or depression	10 year social functioning	LIFE Social Functioning	7.8	13.0	Squared multiple R
Martin et al., 2021	321	First-admission psychosis	20 year diabetes onset	Diabetes	5.0	10.0	none
Martin et al., 2021	317	First-admission psychosis	20 year education attainment	Educational attainment	6.0	10.0	none
Morey et al., 2012	668	Treatment seekers with personality disorder and/or depression	10 year medications	Number of medications taken at 10 year follow-up	3.2	9.0	Squared multiple R
Martin et al., 2021	323	First-admission psychosis	20 year EEG (P300)	P3a amplitude	1.0	7.0	none
Martin et al., 2021	322	First-admission psychosis	20 year EEG (mismatch negativity)	Duration mismatch negativity	3.0	6.0	none
Morey et al., 2012	668	Treatment seekers with personality disorder and/or depression	10 year suicide attempts	Number of suice attempts by 10 year follow-up	6.8	5.3	Squared multiple R

We selected non-redundant measures of biomarkers, functioning, service utilization, and clinical status from these studies. AUC = area under the curve. SLOF = Specific Levels of Functioning scale. PHQ-9 = Patient Health Questionnaire, Depression Module. WHO-DAS = World Health

Organization's Disability Assessment Scale II. UPSA = UCSD Performance-based Skills Assessment. SOFAS = Social and Occupational Functioning
Assessment Scale. B-SNIP = Bipolar- Schizophrenia Network on Intermediate Phenotypes. AUC was transformed to r and then squared to obtain variance explained (Rice & Harris, 2005).

Supplemental Table 2. Clinician ratings of HiTOP and DSM

This system is useful for…	DSM-5			HiTOP		
	Disagree	Neutral	Agree	Disagree	Neutral	Agree
building a therapeutic alliance	33%	67%	0%	0%	33%	67%
selecting a treatment	22%	33%	44%	0%	11%	89%
assessing probable prognosis	0%	33%	67%	0%	0%	100%
educating patients and/or families about diagnosis	11%	11%	78%	0%	11%	89%
gathering information for necessary documentation	0%	11%	89%	11%	0%	89%
communicating with other health care professionals	0%	11%	89%	0%	11%	89%

Note: Anonymous survey of nine clinicians who completed the HiTOP-DAT workshop.