Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): I. Psychosis superspectrum

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The Hierarchical Taxonomy of Psychopathology (HiTOP) is a scientific effort to address shortcomings of traditional mental disorder diagnoses, which suffer from arbitrary boundaries between psychopathology and normality, frequent disorder co-occurrence, heterogeneity within disorders, and diagnostic instability. This paper synthesizes evidence on the validity and utility of the thought disorder and detachment spectra of HiTOP. These spectra are composed of symptoms and maladaptive traits currently subsumed within schizophrenia, other psychotic disorders, and schizotypal, paranoid and schizoid personality disorders. Thought disorder ranges from normal reality testing, to maladaptive trait psychoticism, to hallucinations and delusions. Detachment ranges from introversion, to maladaptive detachment, to blunted affect and avolition. Extensive evidence supports the validity of thought disorder and detachment spectra, as each spectrum reflects common genetics, environmental risk factors, childhood antecedents, cognitive abnormalities, neural alterations, biomarkers, and treatment response. Some of these characteristics are specific to one spectrum and others are shared, suggesting the existence of an overarching psychosis superspectrum. Further research is needed to extend this model, such as clarifying whether mania and dissociation belong to thought disorder, and explicating processes that drive development of the spectra and their subdimensions. Compared to traditional diagnoses, the thought disorder and detachment spectra demonstrated substantially improved utility: greater reliability, larger explanatory and predictive power, and higher acceptability to clinicians. Validated measures are available to implement the system in practice. The more informative, reliable and valid characterization of psychosis-related psychopathology offered by HiTOP can make diagnosis more useful for research and clinical care.

Key words: HiTOP, psychosis, thought disorder, detachment, schizophrenia, psychotic disorders, personality disorders, psychoticism, introversion, clinical utility

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The Hierarchical Taxonomy of Psychopathology (HiTOP) consortium was formed by psychiatric nosologists to integrate evidence from studies on the organization of psychopathology and outline a system based on these data[1]. This effort is motivated by shortcomings of traditional taxonomies: arbitrary boundaries between psychopathology and normality, diagnostic instability, heterogeneity within disorders, frequent disorder co-occurrence, and inability to account for subthreshold cases. The HiTOP system addresses these problems by: a) defining psychopathology in terms of dimensions of psychological function that range from normal to abnormal, b) identifying dimensions based on observed covariation among signs, symptoms and maladaptive behaviors, and c) combining these primary dimensions into larger spectra.

The dimensional approach resolves the issue of arbitrary boundaries and diagnostic instability, as evidenced by the high test-retest reliability of dimensional psychopathology constructs [2-5]. Also, no patients are excluded from the system, because even individuals with subthreshold symptoms or unusual symptom profiles can be characterized on a set of dimensions. The HiTOP model reduces heterogeneity within constructs by grouping related symptoms together and assigning unrelated symptoms to different dimensions[6-9]. Comorbidity is recognized in this system through assignment of related conditions to the same spectrum. The hierarchical organization allows for a flexible description of a patient in terms of broad spectra or narrow subdimensions, depending on the desired degree of specificity.

The HiTOP system currently includes six higher-order spectra: internalizing, somatoform, disinhibited externalizing, antagonistic externalizing, thought disorder, and detachment[1]. These major dimensions of psychopathology reflect individual differences in a given domain across the entire population. Spectra can be combined into larger superspectra: emotional dysfunction (internalizing and somatoform), externalizing (disinhibited and antagonistic), and psychosis (thought disorder and detachment)[10-14]. Above the superspectra sits the general psychopathology or p factor, a dimension that contains features common to all mental disorders[15,16].

The HiTOP system was derived from a large body of structural research[1,17,18], but its external validity and utility are less established, as previous reviews of these topics had limited scope[19-21]. To address this shortcoming, the Utility Workgroup of HiTOP consortium assembled teams of experts to systematically review evidence on validity and utility of the system. Expert reviews were organized according to the three superspectra. The present paper is the first in this series and focuses on the psychosis superspectrum.

This superspectrum encompasses two spectra: thought disorder and detachment. The thought disorder spectrum describes individual differences that range from conventional and uncreative thinking to perception and cognition that are only tenuously based in reality. It includes both positive symptoms and the personality trait of psychoticism, also known as positive schizotypy[22-27]. The label "thought disorder" aims to capture these diverse elements and is distinct from formal thought disorder (i.e., incoherent thought and discourse), which is one of many symptoms in the spectrum. The detachment spectrum describes individual differences in volition (ranging from energetic pursuit of goals to apathy), sociability (ranging from strong social engagement to disinterest in people), and affective expression (ranging from highly expressive to restricted). This spectrum spans from the personality trait of introversion, to negative schizotypy, to negative symptoms[22,28-32].

The spectra include both maladaptive traits and symptoms. These parallel each other but reflect different timescales. Signs and symptoms reflect the current state, problems that may be acute and transient; whereas maladaptive traits capture typical levels of these problems over many years and are fairly chronic[33,34]. For instance, disorganization symptoms indicate current disturbance in organization or expression of thought and odd behavior, whereas trait peculiarity describes very similar problems but assessed over the lifetime. Indeed, disorganization and peculiarity are closely aligned empirically[35,36]. Furthermore, maladaptive traits change over time, but gradually and slower than symptoms[37-39]. Moreover, traits cover a broader range of individual differences, spanning from healthy to vulnerable to symptomatic[40-42], thus providing useful prognostic and etiologic information to complement symptom-based assessment.

The HiTOP follows a long tradition of models that posited a spectrum spanning from normality to personality pathology to schizophrenia[43-45] and elaborates on them using modern statistical modeling techniques and new evidence. It also builds on the idea of an extended psychosis phenotype, a transdiagnostic entity that includes subclinical psychotic experiences as well as frank psychosis[46-49]. The thought disorder spectrum encompasses this phenotype, and extends it to include trait psychoticism, forming a dimension that spans the entire population. The HiTOP conceptualization of psychotic disorders is also consistent with staging models and clinical high risk approaches[50-53], as HiTOP describes spectra along which people may progress from subthreshold vulnerability to symptoms.

In this paper, we examine the evidence on structural coherence and composition of thought disorder and detachment, and consider the validity and utility of these spectra.

STRUCTURAL EVIDENCE

Composition of major dimensions

The psychosis superspectrum emerges in research on the structure of psychiatric diagnoses[11] and of maladaptive personality traits[54]. It is well-documented as a non-affective dimension of psychosis that encompasses positive and negative symptoms[6-8,55]. This union of positive and negative symptoms or corresponding maladaptive traits has long been recognized clinically in diagnoses of schizophrenia and schizotypal personality disorder. Indeed, these diagnoses were found to define a dimension distinct from the emotional dysfunction and externalizing superspectra[56-62], as summarized in Table 1.

The thought disorder spectrum has been observed in many studies, which defined it primarily by positive symptoms or psychotic experiences[26,63-66]. Moreover, studies of personality pathology consistently find the corresponding psychoticism dimension[67-71]. The detachment spectrum has been reported in multiple studies of mental disorders[11,26,62,71-73]. It emerged in research on psychosis as a distinct dimension of negative symptoms[7,8,30,55,74,75]. Furthermore, detachment has been replicated several times in studies of maladaptive traits[67-70], and its healthy range – introversion – is extensively documented[32,71,76-78].

Overall, structural studies suggest that schizophrenia, schizophreniform disorder, schizoaffective disorder, and schizotypal and paranoid personality disorders reflect elevations on both thought disorder and detachment spectra (Table 1). Other psychotic disorders are linked specifically to the thought disorder spectrum, whereas schizoid and avoidant personality disorders are linked solely to detachment.

Several studies considered obsessive-compulsive disorder and, although some linked it to the psychosis superspectrum[60,63], the majority found that it falls within the emotional dysfunction superspectrum[26,57,58,62,66]. Two studies placed dependent personality disorder on detachment[62,73], but meta-analyses of personality disorders and maladaptive traits located dependent personality disorder on internalizing[70,79,80]. One study linked dysthymic disorder to detachment[73], but this is inconsistent with extensive evidence placing depressive disorders on internalizing[1]. Consequently, these three disorders and their symptoms will not be considered here.

Dissociative disorders were linked to the thought disorder spectrum in only one study[63]. However, a substantial literature has documented close ties of dissociative disorders with psychotic disorders and psychoticism[81-83]. These studies provided evidence of comorbidity, symptom overlap, and common risk factors that support the placement of dissociation within the thought disorder spectrum. In research on the structure of personality pathology, dissociation symptoms have been placed on psychoticism[84,85]. Hence, we assigned dissociation to thought disorder on a provisional basis, pending further structural research.

Bipolar I disorder was linked to thought disorder in three studies[56,58,60] and to internalizing in one[61]. Several other studies reported an association between mania and internalizing, but did not examine an association between mania and thought disorder[86-89]. We provisionally included mania in thought disorder, but it remains uncertain whether mania is better placed on internalizing, blends features of both spectra, or forms a dimension distinct from them.

Table 1 Higher-order structures that included psychotic disorders or schizotypal personality disorder in interview-based studies

	Sample size	Sample type	Schizophrenia	Schizotypal PD	Psychosis, psychotic experiences	Bipolar I	Paranoid PD	Schizoid PD	Avoidant PD	Dependent PD	Dysthymic disorder	Dissociative disorder	OCD
Psychosis superspectrum													
Wolf et al[61]	205	Inpatient	+			–							
Markon et al[62]	8,405	Community		+	+		+	+	–				–
Kotov et al[58]	2,900	Outpatient		+	+	+	+	+					–
Kotov et al[57]	469	Inpatient	+	+									–
Keyes et al[56]	34,653	Community		+		+	+	+	+				
Caspi et al[60]	1,000	Community	+			+							+
Shanmugan et al[59]	9,498	Community youth	+		+								
Total	57,130		4/4	4/4	3/3	3/4	3/3	3/3	1/2	0/0	0/0	0/0	1/4
Thought disorder spectrum													
Chmielewski[63]	381	Outpatient		+	+							+	+
Wright et al[66]	8,841	Community			+								–
Wright & Simms[26]	628	Outpatient		+	+		–						–
Schaefer et al[65]	2,232	Community adolescents			+								
de Jonge et al[64]	15,499	Community			+								
Total	27,581		0/0	2/2	5/5	0/0	0/1	0/0	0/0	0/0	0/0	1/1	1/3
Detachment spectrum													
Markon et al[62]	8,405	Community							+	+			
Roysamb et al[73]	2,794	Community						+	+	+	+		
Forbes et al[11]	2,900	Outpatient		+				+	+				
Wright & Simms[26]	628	Outpatient		–				+	–				
Total	14,727		0/0	1/2	0/0	0/0	0/0	3/3	3/4	2/2	1/1	0/0	0/0

PD – personality disorder, OCD – obsessive-compulsive disorder

Role of maladaptive traits

Psychoticism and detachment traits emerged from research on personality pathology, and are included in the DSM-5 alternative model of personality disorders. These dimensions were also found in research on schizotypy, a personality vulnerability to psychotic disorders, which identified distinct positive and negative schizotypy dimensions[90]. Similar dimensions emerged in research on clinical high risk for psychosis, which described positive and negative risk syndromes[91]. Positive schizotypy and positive risk syndrome were found to map onto psychoticism, and negative schizotypy and negative risk syndrome onto detachment[92,93].

Psychoticism shows clear links to schizotypal personality disorder, dissociation, and psychotic disorders[23,26,85,94,95]. Detachment has a specific association with schizoid personality disorder, as well as weaker links to avoidant and schizotypal personality disorders[23,26,80,94,95]. Both traits are tightly linked to schizophrenia[24,96]. Overall, cross-sectional data suggest that these traits underpin thought disorder and detachment spectra.

These relationships are further underscored by evidence that psychoticism and detachment predict first onset of psychosis and negative symptoms[41,97,98], consistent with the view that these traits are precursors to symptoms[43]. Psychosis onset is predicted more by psychoticism than detachment, and detachment can be considered a vulnerability trait for negative symptoms and schizophrenia[98]. These findings are consistent with high rates of future schizophrenia onset in treatment-seeking samples with schizotypal personality disorder[99,100].

Detachment is aligned with introversion and can be considered its more extreme and maladaptive expression[32,78,101]. In psychotic disorders, positive symptoms were found to align with psychoticism, and negative symptoms with detachment and introversion[22,28,29,41,102,103]. Thus, symptoms and traits jointly define HiTOP spectra. Some theories of relations between personality and psychotic disorders hypothesized a latent discontinuity, with risk of psychosis limited to a qualitatively distinct subgroup[43,104]. Studies of this question produced mixed results, and further research is needed to determine whether any discontinuities exist in the psychosis superspectrum[105,106].

Overall model

Subdimensions have been consistently identified within the spectra. Thought disorder symptoms can be decomposed into reality distortion (hallucinations and delusions) and disorganization (formal thought disorder and bizarre behavior) dimensions[107-109]. Dissociation and mania can be added as provisional dimensions[56,58,60,63,83]. The spectrum also includes facets of psychoticism trait: peculiarity (odd appearance, speech and behavior), unusual beliefs (unfounded or magical), unusual experiences (perceptual distortions, depersonalization and derealization), and fantasy proneness (vivid imagination and tendency to become engrossed in inner experiences)[25,68,78,110].

Detachment symptoms include inexpressivity and avolition dimensions[7,111-113]. Trait facets of detachment comprise emotional detachment (difficulties in the experience, description and expression of feelings), anhedonia (deficits in positive emotions and energy), social withdrawal (avoidance of interpersonal interactions due to disinterest), and romantic disinterest (lack of interest in sex and intimacy)[25,68,78]. Further subdivisions are possible[74,114,115], but are not yet established.

The overall model of major dimensions and their components is summarized in Figure 1. It extends the current HiTOP model[1] in several respects based on additional evidence. DSM-5 diagnoses are not included in HiTOP, but they are comprised of the same features (signs, symptoms and traits). Consequently, spectra can be observed in patterns of comorbidity among disorders, thus helping to define these major dimensions of HiTOP. In the present paper, we focus on validity and utility of thought disorder and detachment spectra, although with the understanding that they contain multiple trait and symptom subdimensions.

VALIDITY EVIDENCE

The HiTOP Utility Workgroup examined validity of thought disorder and detachment spectra against nine criteria: behavior genetics, molecular genetics, environmental risk factors, cognitive and emotional processing abnormalities, neural substrates, biomarkers, childhood temperament antecedents, illness course, and treatment response.

These validators are based on the eleven criteria outlined by the American Psychiatric Association's Diagnostic Spectra Study Group for the meta-structure project, the goal of which was to identify coherent clusters of mental disorders[116]. The meta-structure project criteria were an extension of the validators proposed by Robins and Guze[117]. Among the eleven criteria, we did not consider "comorbidity" and "symptom similarity", as these are ensured in derivation of the HiTOP model. Indeed, the spectra are defined by disorder and symptom co-occurrence.

We sought to determine whether thought disorder and detachment spectra are coherent on each validator; that is, if psychopathology included in the spectrum has similar associations with the criterion. We examined literatures on symptom dimensions and traits included in the two spectra. Related disorders were considered also, as existing validity research largely focused on diagnostic groups. We found that data on some conditions (e.g., dissociation) are very limited, and we do not discuss them in this validity section.

Behavior genetic evidence

Evidence for a genetically coherent psychosis superspectrum was originally observed in family studies. This research found that relatives of people with schizophrenia have highly increased rates of non-affective psychoses, schizoaffective disorder, schizotypal and paranoid personality disorders, as well as schizophre-

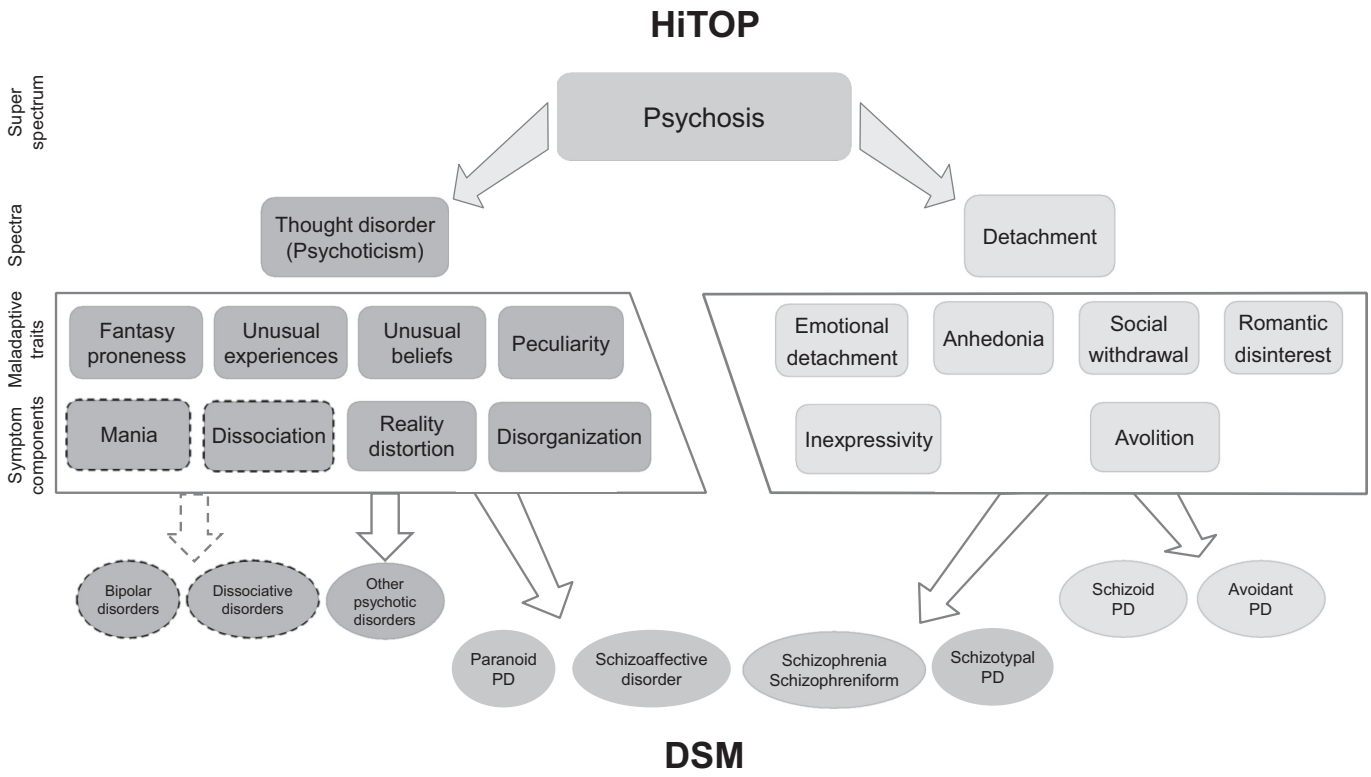

Figure 1 Dimensions within the Hierarchical Taxonomy of Psychopathology (HiTOP) psychosis superspectrum. PD – personality disorder

nia[118]. Twin research identified a similar genetic factor common to schizotypal, schizoid and paranoid personality disorders[119].

Evidence for the thought disorder spectrum is even more compelling. Schizophrenia, bipolar I disorder, and schizoaffective disorder have shown high level of genetic overlap across studies that used family, adoption and twin designs[120-123]. This pattern supports the genetic coherence of the thought disorder spectrum. Moreover, family data suggest that this spectrum is distinct from genetic liabilities to internalizing and externalizing problems[123]. Importantly, twin modeling revealed that genetic risk for thought disorder is continuous, such that clinical and subclinical levels of the spectrum reflect the same genetic liability[124]. Also, directly measured psychoticism was found to be substantially heritable[125,126].

The detachment spectrum has been linked to schizophrenia in family studies. This research established that the detachment trait is elevated in relatives of people with schizophrenia compared to relatives of healthy probands or probands with mood disorders, indicating a specific connection between detachment and schizophrenia[127]. Moreover, schizophrenia showed stronger familial associations with detachment than with psychoticism[127].

Twin studies supported the genetic coherence of the detachment spectrum. They identified a genetic factor common to schizoid and avoidant personality disorders[128,129], and potentially to schizotypal personality disorder and dysthymic disorder as well[128]. The genetic detachment factor also emerged in twin studies of maladaptive traits[129]. Furthermore, a twin study of normal and maladaptive personality found a genetic factor defined by detachment, schizoid and avoidant personality disorders, as well as introversion (and also low openness)[130]. This factor was distinct from genetic liabilities to other forms of personality pathology. Also, directly measured detachment shows considerable heritability[125,126].

Overall, this research provided clear evidence of two coherent and distinct genetic factors – aligned with psychoticism and detachment – that underpin the proposed psychosis superspectrum. Moreover, the superspectrum itself is highly heritable, with 73% of variance due to genetic influences[131].

Molecular genetics

Molecular genetic research strongly supports the genetic coherence of the thought disorder spectrum. Genome-wide association studies (GWAS) of schizophrenia and bipolar disorder found that many common genetic variants, each with a small effect size, contribute to risk for both conditions[132-134]. Indeed, the genetic correlation between schizophrenia and bipolar disorder is very high (rg = .70)[132,135]. This genetic overlap is further confirmed by correlation between their polygenic risk scores[136,137]. Notably, bipolar I disorder relates more strongly to schizophrenia than to depression (rg = .71 vs. .30), whereas the opposite is true for bipolar II disorder (rg = .51 vs. .69)[132]. Overall, molecular genetic evidence indicates a special connection between mania

and thought disorder. Reality distortion – including subthreshold symptoms – and disorganization were associated with the genetic risk for schizophrenia, but these effects were modest and not specific[138-140].

The genetic coherence of the detachment spectrum has not been studied, but genetic links between detachment and thought disorder dimensions have been documented, which supports the psychosis superspectrum. Schizophrenia polygenic risk score was found to predict negative symptoms both in patients and in the general population[140-143]. Also, anhedonia and low sociability demonstrated moderate genetic correlations with schizophrenia[144,145].

Beyond common genetic variants, approximately 2-3% of schizophrenia patients have rare variants with substantial effect on the risk for the disorder, such as copy number variants (CNVs)[146]. CNVs have not been consistently implicated in risk for the psychosis superspectrum aside from schizophrenia. However, one study found elevated burden of CNVs in schizoaffective disorder[147] and another found it in individuals with psychotic experiences[138].

In sum, molecular genetic research supports the coherence of the thought disorder spectrum and the psychosis superspectrum. Bipolar I disorder has been clearly linked to thought disorder on the genetic level. However, the genetic structure of detachment and lower-order dimensions in both spectra remain to be explicated.

Environmental risk factors

A wide range of environmental risk factors have been identified for schizophrenia and the psychosis superspectrum broadly[148]. We focus here on the most replicated effects.

Ethnic minorities and migrants experience high rates of nonaffective and affective psychotic disorders[149-153]. In the general population, ethnic minority status was associated with elevated psychoticism[48,154]. In patients, minority status was correlated with more severe reality distortion, disorganization, and negative symptoms, although this last effect is weaker and less consistent[8,155-157]. Multiple processes may explain effect of minority status, such as high social adversity, but are not yet fully understood[153].

The incidence of psychotic disorders is considerably higher in urban than rural areas[158,159]. In patients with first-episode psychosis, urbanicity was associated with more severe reality distortion and disorganization symptoms[156]. In the general population, it was associated with elevated psychoticism[160-162]. Links between urbanicity and detachment have not been studied. The effect of urbanicity on psychosis is unlikely to be explained by methodologic confounds, such as social drift, but it is uncertain which of the many exposures common in urban environments explain elevated risk[158]. Importantly, the effect appears not to hold in low- and middle-income countries, where urbanicity may index greater access to resources[163].

Childhood adversity and trauma is a potent risk factor for nonaffective and affective psychotic disorders[164,165]. This association was observed at all levels of thought disorder, from psychoticism to symptoms to diagnosis[166]. Childhood adversity is also a risk factor for bipolar I disorder[167]. Childhood adversity is clearly linked to reality distortion symptoms, while its association with negative symptoms is less consistent and understudied, and data on disorganization are lacking[168]. With regard to traits, childhood adversity is consistently associated with psychoticism, and preliminary evidence supports a link to detachment[169,170].

Cannabis use was found to predict onset of psychotic symptoms and psychotic disorders[171]. In the general population, it was associated with both elevated psychoticism and detachment, although the latter effect was weaker[48,172-174]. In patients, cannabis use was associated with more severe reality distortion symptoms and was not consistently linked to other symptoms[175-179].

Overall, these data indicate common risk factors for each spectrum. Ethnic minority status and cannabis use were linked to both detachment and thought disorder spectra, especially to the latter. Urbanicity and childhood adversity were linked more specifically to the thought disorder spectrum.

Cognitive and emotional processing abnormalities

In schizophrenia, schizoaffective disorder, bipolar I disorder, and schizotypal personality disorder, cognitive deficits were documented in all domains: sensorimotor, attention, learning and memory, executive functions, language, and social cognition[180-184]. These deficits were most pronounced in schizophrenia, but the other disorders showed a similar, although less extreme, profile of cognitive impairment[185-188]. With regard to dimensions, negative and disorganized symptoms were linked to all aforementioned deficits, whereas reality distortion was essentially unrelated to cognitive impairment[189-191]. Similarly, among maladaptive traits, detachment showed the strongest association with a range of cognitive deficits[192-194]. The reported effects were weaker for traits than for symptoms, likely because nearly all personality studies were performed in non-clinical populations with a limited range of psychopathology.

Schizophrenia, schizoaffective disorder, and schizotypal personality disorder also showed deficits in ability to anticipate and seek pleasurable experiences[31,182]. Behavioral deficits were documented in reward processing tasks including delay discounting, reinforcement learning, and emotion-based decision making[195-199]. These effects were specific to detachment and largely unrelated to thought disorder[31]. In contrast, mania was associated with hypersensitivity to rewards[200,201].

Overall, research consistently indicates that cognitive deficits are linked to detachment and disorganization, reward processing deficits are specific to detachment, reward hypersensitivity is specific to mania, and none are clearly related to reality distortion. HiTOP conceptualization of psychopathology can help to isolate associations with cognition that are obscured in heterogeneous diagnoses.

Neural substrates: neuroimaging

Neural correlates of the psychosis superspectrum have been identified using various imaging modalities, and the number of

potential substrates is very large. Here we focus on the most robust findings that were examined across multiple conditions. We discuss the thought disorder spectrum and then the detachment spectrum.

The thought disorder spectrum is associated with structural deficits in numerous brain regions[182]. The most replicated finding is smaller hippocampal volume in schizophrenia, schizoaffective disorder, bipolar disorder, and schizotypal personality disorder[202-205]. This was also observed in relatives of people with schizophrenia[206]. Furthermore, smaller hippocampal volume was associated with severity of reality distortion symptoms[205]. Of note, other volumetric differences have been linked to multiple disorders in the spectrum, but research on them is more limited[203,207-210].

Structural connectivity abnormalities were reported throughout the thought disorder spectrum. Small splenium of the corpus callosum was found in patients with schizophrenia, schizoaffective disorder, and psychotic bipolar disorder, as well as in their relatives[211]. This indicates weak connectivity among multiple brain regions, including the hippocampus. Moreover, smaller splenium was associated with worse reality distortion symptoms[211]. Studies using fractional anisotropy found that low white matter integrity in the genu of the corpus callosum and in the posterior cingulum fiber bundle are present in both schizophrenia and bipolar disorder, as further evidence of common abnormalities in structural connectivity[212].

Functional connectivity alterations were observed in thought disorder as well. The most replicated finding is hypoconnectivity of multiple brain networks in schizophrenia, schizoaffective disorder, and bipolar disorder[213-215]. Connectivity patterns differ across conditions, but show substantial overlap, especially hypoconnectivity within the default mode network and cingulo-opercular network. This hypoconnectivity was found across psychotic disorders and in people with psychotic experiences[216-218]. Similarly, poor efficiency in the connectivity of the cingulo-opercular network was observed across psychotic disorders[219] and was associated with psychoticism in the general population[218].

The detachment spectrum has been studied less extensively, but a few promising findings have emerged. A large study not only found a widespread cortical thinning in schizophrenia, but also linked it to negative symptoms, whereas correlations between positive symptoms and cortical thickness were much more limited[208]. Also, negative symptoms were associated with smaller volume of left caudate nucleus, supporting involvement of the ventral striatum dysfunction in detachment[220].

Functional magnetic resonance imaging supported this interpretation, revealing bilateral hypoactivation of the ventral striatum during potential reward anticipation in schizophrenia, other psychotic disorders, and clinical high risk samples[221]. Importantly, this hypoactivation was associated with negative and not positive symptoms. These findings are consistent with the role that the ventral striatum plays in motivation and reward processing[222,223], in line with emotion deficits described earlier.

With regard to connectivity, negative symptoms were associated with low white matter integrity in many brain regions, including the corpus callosum[224], and with hypoconnectivity within the default mode network[216]. However, connectivity research is fairly preliminary, and detachment traits and related personality disorders have not been studied.

In addition, abnormal activation patterns within the dorsolateral prefrontal cortex and connected executive control regions during working memory tasks were consistently found in schizophrenia and clinical high risk states[225,226]. Moreover, these abnormalities were associated with the psychosis superspectrum in the general population[227]. Some evidence suggests that this association is with detachment rather than thought disorder, consistent with behavioral data on working memory performance and negative symptoms[190,227,228]. However, specificity remains uncertain, and abnormal activations during working memory may be a marker of the overarching superspectrum.

Neural substrates: neurophysiology

Neurophysiological measures have provided further understanding of neural processes underpinning the superspectrum. Deficits in basic inhibitory processes have been documented in schizophrenia, schizotypal personality disorder, and bipolar disorder[182,229,230]. These processes include sensory gating (P50 amplitude), prepulse inhibition, and antisaccade eye movement. They suggest poor selective attention and inhibition, resulting in sensory and cognitive overload, which can contribute to psychoticism and positive symptoms[230].

Electroencephalography probes neural dysfunction more directly. Abnormalities in P300 amplitude and latency as well as mismatch negativity have been established in schizophrenia, clinical high risk states, schizotypal personality disorder, and bipolar disorder[182,192,231-234]. This pattern suggests that P300 and mismatch negativity track thought disorder, but direct evidence of specificity is limited, and they may prove to be markers of the general psychosis superspectrum.

A relatively new marker is error-related negativity, a key measure of early performance monitoring associated with function of the anterior cingulate[235]. This measure is blunted across psychotic disorders as well as in schizotypal personality disorder and clinical high risk groups[236]. This blunting appears to be specific to detachment rather than thought disorder[237,238].

Biomarkers

Blood-based measures are emerging as potential biomarkers for the psychosis superspectrum. Metabolic dysregulations – such as high glucose and triglyceride levels – can be found in both schizophrenia and bipolar disorder[239,240], but they are in part related to the impact of some antipsychotic medications. Pro-inflammatory markers – including interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL1-RA, and sIL-2R – were found to be upregulated both in schizophrenia and bipolar disorder[241], but this profile is not specific, as depression and other mental disorders show similar abnormalities[241,242].

Overall, proteomics research identified 77 proteins altered in

both schizophrenia and bipolar disorder, and only 21 of them were also altered in depression[243]. Many of these effects were observed only in a single study. However, alterations in brain-derived neurotrophic factor (BDNF) have been consistently replicated[244,245]. This is a neurotrophin that modulates neuronal development and plasticity, and its blood levels have been found to be decreased in both schizophrenia and bipolar disorder.

Gene expression has been studied in postmortem brains, and transcriptomic profiles of schizophrenia and bipolar disorder have been found to be very similar[246-248]. The largest study to-date reported that cortical transcriptomic profiles of schizophrenia and bipolar disorder are much more similar to each other (rs = .70) than to profiles of major depressive disorder, alcohol use disorder, and autism (rs = –.06 to .43)[249]. The common thought disorder transcriptomic profile includes alterations in multiple pathways, such as genes controlling immune function[247,249,250].

Gene expression in the brain is not a practical biomarker, but expression in the peripheral blood tends to mirror expression in the brain[251]. Indeed, blood transcriptomic profiles of schizophrenia and bipolar disorder were found to be similar and include altered expression of immune system genes[252,253]. Relations between gene expression and symptom dimensions are understudied, but preliminary evidence suggests that altered expression of immune genes is specific to psychoticism, whereas expression of mitochondrial genes is associated with detachment[253]. Analyses of DNA methylation in blood revealed similar profiles in schizophrenia and bipolar disorder[254], but findings differed across studies and were confounded by methodological differences, so should be considered preliminary.

Overall, studies of immune function, proteomics and transcriptomics suggest that schizophrenia and bipolar disorder share a biological signature. This signature may be common across the thought disorder spectrum. However, conclusions have been moderated by methodological limitations of existing studies, and other disorders and dimensions relevant to the psychosis superspectrum are understudied.

Childhood temperament antecedents

Longitudinal data on links between childhood temperament and adult psychosis superspectrum are very limited. A few studies assessed psychoticism in childhood – using informant reports – and found that it predicted self-reported psychoticism in adolescence and adulthood[255-257]. In youths, both psychoticism and detachment were found to predict future onset of psychotic disorders as well as of schizotypal and schizoid personality disorders, with some evidence that psychoticism is a risk factor primarily for psychotic symptoms and detachment for negative symptoms[36,41,97,98,258,259].

This evidence suggests that the psychosis superspectrum has roots in childhood psychoticism and detachment traits, with onset of disorders resulting from progression along the continuum toward greater severity, as has been found for progression from psychotic experiences to disorder[260-262]. However, existing knowledge is limited by reliance on clinical high risk or treatment-seeking samples and lack of data on preschool temperament. Also, the specificity of the observed links is uncertain, as most studies examined only a small set of traits and disorders.

Illness course

Chronic course is a hallmark of schizophrenia, as only a small minority of cases achieve durable recovery[263]. We examined whether chronicity characterizes the entire superspectrum. Recovery is typically defined by both symptom remission and good functioning[264], so we considered both in turn. The rate of symptom remission in schizophrenia following treatment is approximately 37%, largely due to high chronicity of negative symptoms[265]. Likewise, schizotypal and avoidant personality disorders show remission rates of 23-47% two years after diagnosis[266]. In contrast, 84% of first-admission patients with mania achieve remission within a year[267].

Functional outcome follows the same pattern. First-episode schizophrenia results in moderate illness severity at follow-up, with a mean Global Assessment of Functioning (GAF) score of 56 [268]. Schizotypal personality disorder has a similar outcome, with a mean GAF score of 53 at two-year follow-up[269]. In avoidant personality disorder, two-year outcome is somewhat better, with a mean GAF score of 62, indicating mild severity[269]. Bipolar disorder shows the best outcome, with a mean GAF score of 70 two years after first hospitalization[270,271].

Studies that measured the spectra directly found that psychoticism and detachment are impressively stable over time, with 10-year stability correlations of .66 and .82, respectively[272]. Moreover, psychoticism, trait detachment, and especially negative symptoms are associated with poor functioning and predict worse global outcomes even ten years later[41,273-275]. Positive symptoms appear to predict worse functioning in the general population[260], but not in patients with psychotic disorders, where negative symptoms account for impairment[276]. This highlights the greater role of detachment than thought disorder in functioning. Overall, the two spectra show high chronicity and so do many conditions related to them, with the notable exception of mania.

Treatment response

The thought disorder spectrum shows a common response to antipsychotics. These medications are efficacious for reality distortion and disorganization symptoms across psychotic disorders[277-279]. Antipsychotics also treat manic episodes[280]. Moreover, emerging evidence suggests that antipsychotics can reduce psychoticism in patients who do not have frank psychosis[281]. However, antipsychotics are much less efficacious for the detachment spectrum, such as for negative symptoms, and observed benefits may be limited to secondary negative symp-

toms[282]. Tentative evidence suggests that neuromodulation techniques providing stimulation to specific neural networks can improve negative symptoms[283], but this research is still limited.

The thought disorder spectrum shows a common response to psychotherapy. Cognitive behavioral therapy (CBT) was found to improve positive symptoms compared to treatment-as-usual both at the end of treatment and at follow-up, but it does not outperform other therapies or active control[284]. Other emerging treatments may be more efficacious. Acceptance and commitment therapy (ACT) and meta-cognitive therapy both have shown moderate beneficial effects for positive symptoms, although no significant effects for negative symptoms[284]. Functional behavioral assessment-based interventions appear to be effective for disorganization symptoms across disorders[285].

The detachment spectrum shows a common response to social skills training, which reduces negative symptoms[286-289] and detachment traits[290]. These effects persist after the end of treatment[286] and reduce the probability of transitioning from schizotypal personality disorder to psychotic disorder[291]. Cognitive remediation, a behavioral intervention aimed to improve cognitive processes and not targeting symptoms directly, has been nevertheless found to reduce negative symptoms compared to treatment-as-usual, both at the end of treatment and at follow-up[292]. CBT is efficacious for reducing negative symptoms across psychotic disorders when compared to treatment-as-usual, both at the end of treatment and at follow-up[284,287].

Overall, CBT is an efficacious treatment for both spectra and, indeed, many other forms of psychopathology. In contrast, antipsychotics, ACT and meta-cognitive therapy are relatively specific to the thought disorder spectrum, whereas social skills training and cognitive remediation are relatively specific to the detachment spectrum. Social skills training is efficacious for both detachment symptoms and traits, and emerging evidence suggests that antipsychotics may be efficacious for trait psychoticism as well as frank psychosis. Much less is known about treatment for lower-order dimensions, although social skills training may be particularly efficacious for avolition[293], and functional behavioral assessment-based interventions for disorganization[285].

Summary of validity evidence

Our review of validity evidence is summarized in Table 2. It indicates both substantial coherence within each spectrum and overlap between spectra, which supports validity of the superspectrum. However, the two spectra show more differences than similarities, with 15 validators specific to thought disorder, six to detachment, and 12 common to both.

Of note, blank cells in Table 2 indicate lack of robust evidence, but not necessarily lack of an effect. So, similarities within and between the spectra may be stronger than they appear now. In particular, research is very limited on schizoid and avoidant personality disorders.

Importantly, many of the validators examined are not specific to the psychosis superspectrum. For example, childhood adversity, pro-inflammatory markers, and response to CBT have been linked to emotional dysfunction and externalizing superspectra as well[56,241,242,294,295].

Mania stood out on several validators. Unlike other conditions in the superspectrum, bipolar I disorder tends to have episodic course, often shows good functioning between episodes, and manifests hypersensitivity to rewards. On the other hand, bipolar I disorder is similar to other conditions in the spectrum on numerous other validators, consistent with the view that mania belongs on the thought disorder spectrum, albeit with certain distinguishing features.

Overall, validity findings agree with the structural evidence. This suggests that the HiTOP characterization of psychotic disorders and related personality disorders can provide an informative guide to researchers and clinicians.

UTILITY EVIDENCE

The HiTOP has been compared to traditional diagnostic approaches with respect to reliability, explanatory power, prognostic value, and clinical utility.

Reliability is an essential requirement for a nosology, as an unreliable diagnosis cannot convey useful information. The DSM-5 field trials found an inter-rater reliability (kappa coefficient) of .46 for schizophrenia, .50 for schizoaffective disorder, and .56 for bipolar I disorder[296], which indicates only mediocre agreement between diagnosticians. In these field trials, clinicians also rated positive symptoms as a single item on a 5-point scale, which, despite its brevity, improved reliability to .65[297]. Patients' self-ratings of psychosis on a dimensional measure were even more reliable, with coefficients ranging from .72 to .79[297]. This pattern suggests that dimensional scores retain more useful information than categorical ratings, consistent with extensive prior research[2].

Of note, a field study of ICD-11 reported higher inter-rater reliabilities than DSM-5 field trials, but it used a less stringent design, making high reliability easier to achieve[298].

Psychoticism and detachment demonstrated high reliability in patients (McDonald's omega = .87 and .75, respectively)[299] and even higher reliability in the general population[300]. They also showed high short-term stability, with 2-week test-retest correlations ranging from .81 to .89[301,302], and impressive long-term reliability, with 17-month test-retest correlations ranging from .62 to .74[39]. The overall meta-analytic reliability estimates were .81 for thought disorder and .85 for detachment[2].

In direct comparison, reliability of DSM diagnoses was inferior to HiTOP dimensions, with 2-week stability of .63 for paranoid, .62 for schizoid, .44 for schizotypal, and .63 for avoidant personality disorders, compared to .88 for psychoticism and .89 for detachment[301]. Overall, HiTOP offers >50% improvement in reliability over the DSM in characterizing psychosis-related psychopathology.

Table 2 Validators of the thought disorder and detachment spectra

	Both spectra		Thought disorder spectrum			Detachment spectrum				
	Schizophrenia	Schizotypal PD	Positive symptoms, psychotic experiences	Trait psychoticism	Bipolar I	Negative symptoms	Trait detachment	Schizoid PD	Avoidant PD	Summary of specificity
Genetics										
Family/twin psychoticism	+++			+	+++					T
Family/twin detachment	+++	+					+++	+++	+++	D
Polygenic risk to schizophrenia	+++		+		+++	++	+			B
Burden of copy number variants	+++		+							T
Environment										
Ethnic minority status	+++		+++	+		++				B
Living in urban environment	+++		+++	+						T
Childhood adversity	+++		+++	+++	++	+	+			T
Heavy cannabis use	++		++	+++			++			B
Cognition/Neurobiology										
Cognitive deficits	+++	++			+++	+++	++			B
Reward processing deficits	+++	++			–	+++				D
Small hippocampal volume	+++	+++	++		+++					T
Low white mater integrity in CC	+++		+		+++	+				T
Functional hypoconnectivity	+++		+++	+	+++	++				B
Hypoactive ventral striatum	++					++				B
Altered activation of executive system	+++		++	+		++				B
Cortical thinning	++					++				D
Inhibitory deficits	+++	+++			++					T
Blunted P300	+++	++	++		++					T
Blunted mismatch negativity	+++	++	++		++					T
Blunted error-related negativity	+++	++				+				D

Table 2 Validators of the thought disorder and detachment spectra *(continued)*

	Both spectra		Thought disorder spectrum			Detachment spectrum				
	Schizophrenia	Schizotypal PD	Positive symptoms, psychotic experiences	Trait psychoticism	Bipolar I	Negative symptoms	Trait detachment	Schizoid PD	Avoidant PD	Summary of specificity
Biomarkers										
Pro-inflammatory markers	+++				++					T
Reduced BDNF blood levels	++				++					T
Transcriptomic schizophrenia profile	++				++					T
Antecedents/Course										
Psychoticism in childhood/adolescence	+	++	+++	++						T
Detachment in childhood/adolescence	+	++	++			++		++		B
High chronicity/stability	+++	+		+	−−−		+		+	B
Poor functional outcome	+++	+	+	+	−−	++	+		+	B
Treatment										
Response to antipsychotics	+++	+	+++	+	+++	++				B
Response to CBT			+++			+++				B
Response to ACT			++							T
Response to meta-cognitive therapy			+++							T
Response to social skills training						++	+			D
Response to cognitive remediation						+++				D

+: some evidence for effect, ++: some replications; +++: repeatedly replicated finding, −: some evidence for reverse effect, −−: some replications; −−−: repeatedly replicated reverse effect, T – linked to thought disorder, D – linked to detachment, B – linked to both, CC – corpus callosum, BDNF – brain-derived neurotrophic factor, CBT – cognitive behavioral therapy, ACT – acceptance and commitment therapy

Explanatory and prognostic power is a particularly valuable feature of diagnosis. A meta-analysis found greater validity for dimensional than categorical operationalization of thought disorder and detachment[2]. For thought disorder, the mean validity coefficient (correlation with a validator) was .31 for a category and .42 for a dimension, which indicates a substantial advantage for the latter. For detachment, the advantage was even larger, with mean validity of .32 for a category and .48 for a dimension. However, these estimates were based largely on cross-sectional associations.

A large longitudinal study found the same pattern when comparing ability of personality disorder diagnoses and maladaptive traits included in HiTOP to predict functional and clinical outcomes ten years later[303]. The mean predictive power (R^2) was 0.25 for dimensions vs 0.12 for diagnoses, indicating substantial superiority of the HiTOP approach. However, this study considered all maladaptive traits together and all personality disorders together, and did not report results for psychoticism and detachment separately.

Several studies compared specific dimensions included in the psychosis superspectrum to diagnoses of psychotic disorders by analyzing their cross-sectional associations with validators. Dimensions explained more variance in risk factors[304], psychosis biotypes derived from neurophysiological markers[8], cognitive deficits[305,306], real-world functioning[304,305], and utilization of inpatient services[304]. In contrast, diagnoses outperformed dimensions only in accounting for illness course and utilization of outpatient services[304].

Another study used diagnoses (e.g., schizophrenia and schizotypal personality disorder) to model the psychosis superspectrum, and found that it fully accounted for family risk and illness course over the next ten years, with individual diagnoses contributing no additional variance[57].

Overall, existing research indicates that the HiTOP characterization of psychotic disorders can explain and predict twice as much variance in validators as the DSM, thus increasing value of diagnosis for research and for clinical prognostication.

Although diagnostic reliability and prognostic power are important for clinical applications, a distinct set of considerations may be classified as clinical utility, i.e., the ability of a diagnostic system or diagnostic feature to facilitate implementation, conceptualization, communication, treatment selection/planning, and outcome improvement[307-310]. Existing research relied on practitioner ratings to evaluate utility of a diagnostic system in these domains.

Comparisons of HiTOP and DSM approaches has been largely focused on personality disorders, and global ratings for the system rather than each individual feature. Initial studies asked practitioners to consider vignettes of fictitious cases developed based on the DSM, which confounded results[311,312]. Recent studies requested that practitioners consider actual patients in their caseload, and dimensional approaches generally received higher ratings than DSM categories across most indices of clinical utility[313-317]. Moreover, dimensional measures included in the DSM-5 were rated by 80% of clinicians as moderately to extremely helpful[318].

Overall, existing data strongly support clinical utility of the dimensional approach[319,320]. Nevertheless, it is important to expand studies of clinical utility to include frank psychosis and also compare diagnostic systems on objective criteria, such as fostering better treatment outcomes.

Clinical acceptability of HiTOP is consistent with the aim of the system to formalize and improve existing clinical decision-making practices, as practitioners often rely on presenting signs and symptoms more than on traditional diagnoses[321]. Limitations on the utility of traditional diagnoses are further evident in clinicians forgoing criteria sets and employing abbreviated approaches in making diagnoses[322-324], as well as in extensive off-label prescribing[325]. HiTOP builds on an established practice of dimensional, symptom-oriented and personality-informed case conceptualization to provide clinicians with both a rigorous framework for this approach and validated brief tools to assess these dimensions.

Application of dimensional measures in clinical practice faces practical challenges, including limited reimbursement for assessment, patient burden, and need for categorical decisions (e.g., to treat or wait)[20]. In other fields of medicine, these challenges have not precluded a widespread use of dimensional markers, such as testing levels of metabolites in blood or pathogens in cerebrospinal fluid. Indeed, effective strategies have been developed to justify cost, reduce patient burden, and translate these dimensional metrics into clinical decisions[326,327].

Perhaps, the most direct evidence of clinical utility is the widespread use of dimensional measures in mental health practice. Indeed, rating scales for psychosis and related symptoms have been part of clinical practice and research for decades, including the Brief Psychiatric Rating Scale (BPRS)[328], the Scale for the Assessment of Negative Symptoms (SANS)[329], the Scale for Assessment of Positive Symptoms (SAPS)[330], and the Positive and Negative Syndrome Scale (PANSS)[331]. They have proven clinical acceptability and are required in clinical trials for psychotic disorders[332].

Moreover, programs that treat patients with clinically high risk for psychosis or attenuated psychosis syndrome routinely utilize dimensional symptom measures, especially the Scale of Prodromal Symptoms (SOPS)[91], which is extensively validated and used worldwide[333].

Structural studies identified subscales in each of these measures that align with the HiTOP model[7,91,114,334-337]. Indeed, components of the model were informed by this research.

It is notable that diagnostic manuals now recognize the need for a dimensional characterization of psychosis and related symptoms. The DSM-5 introduced eight dimensional ratings that capture reality distortion (hallucinations and delusions), disorganization (disorganized speech and abnormal psychomotor behavior), negative symptoms (restricted expression and avolition), and mania (manic mood), as well as depression and impaired cognition[74]. The ICD-11 included six dimensional symptom-based qualifiers for psychotic disorders: positive, negative and mania, as well as depressive, psychomotor/catatonic and cogni-

tive impairment[338]. Although these additions are very encouraging, evidence for their clinical utility is currently limited[318].

MEASUREMENT

Several measures are available to apply HiTOP in research and care for psychosis-related psychopathology. We highlight instruments that have both sound psychometric properties and established clinical cutoffs (e.g., categorize severity of psychopathology or define clinically significant change).

Both the PANSS and SANS/SAPS offer psychometrically sound interviewer-rated scales for thought disorder (specifically, positive symptoms) and detachment (negative symptoms)[339,340]. Additional subscales were developed in these measures for reality distortion, disorganization, inexpressivity and avolition, among other dimensions[7,335,337].

Two new interviews were developed for negative symptoms: the Clinical Assessment Interview for Negative Symptoms (CAINS)[111] and the Brief Negative Symptom Scale (BNSS)[341]. Both have psychometrically sound subscales for inexpressivity and avolition[342].

The SOPS is the measure of choice in populations with subthreshold symptoms. It includes four subscales that measure reality distortion, disorganization, negative symptoms, and distress. They largely align with the corresponding scales of the PANSS, SANS and SAPS[343], although factor analytic support for the SOPS subscales has been mixed[344].

The Achenbach System of Empirically Based Assessment (ASEBA)[345,346] includes scales for psychoticism (named thought problems) and detachment (withdrawn). They can be rated by self-report or informant report in both children and adults. These scales have been extensively validated.

Clinical cutoffs are available for the SOPS[333], ASEBA[345,346], and spectra-level scales of the PANSS and SANS/SAPS[339,347]. These measures are ready for both clinical and research use. The component-level scales of the PANSS and SANS/SAPS, as well as the CAINS and BNSS, lack established cutoffs and can be considered research instruments.

Psychoticism and detachment traits can be assessed with high resolution using omnibus measures of personality pathology, such as the Personality Inventory for DSM-5 (PID-5)[348] and the Computerized Adaptive Test of Personality Disorder (CAT-PD)[78]. The Community Assessment of Psychic Experiences (CAPE)[349,350] is a self-report symptom measure, and provides high-resolution assessment of thought disorder and detachment, as well as their subdimensions. These measures are psychometrically sound and have been normed in the general population, and thus can be used clinically to compare a patient's scores to the normal range of functioning. They also assess subdimensions within psychoticism and detachment domains, including all traits in Figure 1[68].

Other measures of these maladaptive traits are available, but are less comprehensive or lack norms and hence are not discussed here. Finally, the DSM-5 and ICD-11 dimensional symptom ratings have not been sufficiently studied to be recommended fully, but they show considerable promise as screening tools and can help to introduce dimensional assessments to settings where thorough evaluations are infeasible.

IMPLICATIONS

The HiTOP offers a reconceptualization of psychosis and related psychopathology to closer align nosology with data. It aims to advance understanding of these conditions in three respects.

First, it underscores that psychotic disorders reflect influences of two major dimensions of psychopathology which are rather distinct with regard to their phenomenology, etiology, prognostic implications, and treatment response. These thought disorder and detachment spectra also show similarities, consistent with the notion of the overarching psychosis superspectrum.

The two-spectra conceptualization agrees with an established observation that some patients primarily suffer from positive symptoms and some are largely burdened by negative symptoms[30,351,352]. Furthermore, this model does not consider psychosis a necessary feature and can characterize people with prominent negative symptoms who have never been psychotic. Of note, internalizing (e.g., depression) and externalizing (e.g., substance abuse) problems are classified on other HiTOP spectra, but are common in psychotic disorders. To characterize a patient fully, all six HiTOP spectra have to be considered, as detailed in previous publications[1,20].

Second, the HiTOP reinforces the emerging consensus that psychosis is on a continuum with normal functioning, maladaptive traits, and subthreshold symptoms[46-49]. The model identifies specific trait manifestations of the spectra: psychoticism and detachment. Elevations on these traits often precede onset of psychosis and are valuable as risk factors. Moreover, levels of psychoticism and detachment vary across the general population, making them more informative targets for etiologic research than psychosis, which is a rare and extreme phenomenon. Overall, the dimensional approach helps to understand how psychosis-related problems are distributed in the population, what processes underpin them, and how preventive interventions can be most effective.

Third, the HiTOP further addresses heterogeneity within psychotic disorders by explicating specific trait and symptom dimensions that constitute the thought disorder and detachment spectra (Figure 1). Included dimensions were established to be internally consistent and distinct, but future research may reveal that more need to be added. In particular, catatonia symptoms and cognitive impairments have not been incorporated into the model.

In the psychosis superspectrum, patients can be represented as profiles of elevations on the corresponding 14 specific dimensions, along with the mean score on the two spectra and on the superspectrum. These dimensions capture both current problems (symptoms) and long-standing problems (maladaptive traits). Validated tools are available to assess these scores by in-

terview, self-report and informant report.

The placement of mania and dissociation on the thought disorder spectrum remains provisional. Dissociation has shown many phenotypic similarities to reality distortion and psychoticism, but the evidence was too limited to include it in our review of validity. Further research is needed to resolve its placement. Mania has been studied extensively and exhibited a profile similar, although generally less extreme, to other thought disorder conditions on numerous validators. The exceptions are course and certain neural substrates. It is possible that mania is a distinct manifestation of a common liability to thought disorder and largely shares etiology and treatment response with non-affective psychosis, although it usually is less disabling. This account remains a hypothesis, as existing data are insufficient to test it definitively.

The HiTOP is a static model at present. Its focus is on characterizing dimensions of psychopathology and accurately assessing a person's current standing on each. However, the hierarchical and dimensional conceptualization is very compatible with developmental models, such as the staging model of psychosis that describes how subthreshold problems evolve into chronic psychosis[51-53]. Once dimensions are identified, the next task is to characterize how patients progress along these dimensions toward greater pathology or improvement.

The understanding of how thought disorder and detachment spectra develop is quite limited at present, although it appears that the core traits are already present in childhood and constitute risk for onset of psychotic disorders. This is consistent with findings for other HiTOP spectra, which received more attention in developmental research[353-355]. Specifically, vulnerabilities can often be observed in childhood, and future disorders tend to emerge out of related vulnerabilities, whereas it is fairly uncommon for psychopathology to shift from one spectrum to another. It is less clear what processes and exposures drive progression along a spectrum to full-blown disorder, which remains a crucial topic for future research[356].

Research implications

The HiTOP model has specific implications for research design, from the sampling, measurement, analytic and conceptual viewpoints.

With regard to sampling, the HiTOP highlights major limitations of case-control studies, which sample people from extreme ends of a dimension. This can maximize statistical power, but has two downsides. First, these analyses exclude people in the middle of the distribution, which makes identified effects not representative of the population. Indeed, this design ignores a sizable proportion of the general population. Second, cases differ from controls in many respects not relevant to the construct of interest, as they are usually recruited from clinical settings, and treatment-seeking is associated with particularly high rates of distress, impairment, comorbidities (including physical ones), and exposure to medication, all of which may confound results.

These limitations of the case-control design are well-known [357,358]. The HiTOP provides an impetus for an alternative design with population-based sampling (perhaps oversampling for high scores). This design is reasonable, even desirable, given the continuous nature of psychopathology and the availability of measures that capture the full range of its manifestations, from normative to subclinical to severe[19]. The population-based strategy can be cost-effective, in that recruitment of cases with first episode psychosis or clinical high risk tends to be slow and costly, whereas high scorers on psychoticism and detachment can be identified rapidly using self-report tools. This design can be further strengthened with follow-up interview-based assessments to evaluate the spectra and their subdimensions with maximum rigor. Another implication is that research on psychotic disorders should not solely focus on reality distortion, but also include participants who are elevated on detachment alone. In general, inclusion criteria for HiTOP-conformant research can be very broad, with the main concern being whether valid assessment can be obtained. Comorbidities and other confounds can be managed statistically provided adequate sample size.

For measurement, HiTOP-conformant measures described earlier promise more reliable and informative assessments than diagnoses. We recommend assessing both maladaptive traits and symptoms, to obtain a comprehensive picture with a modest increase in patient burden, especially if brief and self-administered instruments are used. The spectra can be usually estimated from categorical diagnoses, but it is preferable to measure them directly within HiTOP-conformant instruments, as this maximizes reliability and information obtained[359].

Analytically, HiTOP dimensions can be measured directly and analyzed in the whole sample using conventional statistics. If a diagnostic assessment was completed, it may be useful to test the transdiagnostic nature of relationships of interest, such as whether diagnosis moderates the association between a psychoticism scale and a validator[219]. Latent variable modeling is not required for a HiTOP study, but can be informative. For example, it can facilitate secondary analyses of existing data, where HiTOP-conformant measures were not included, by estimating latent dimensions from standard diagnostic and symptom assessments[7,8,57,59,306].

A conceptual implication is that conditions included in a given spectrum tend to have many commonalities with regard to etiology, clinical features, and treatment. This aspect of the model can be leveraged in two ways. First, the spectra can be studied directly, as they provide more parsimonious and robust phenotypes than individual conditions. Second, effects found for one condition are expected to generalize across the spectrum. This will not be true in every case and should always be confirmed empirically, but can be considered a strong hypothesis.

On the balance, some effects will be specific to narrow dimensions rather than the general spectrum. The HiTOP provides the framework for identifying specific and general features of psychopathology. This hierarchical arrangement can help to understand the role of risk factors, outcomes and treatments across mental disorders. Specificity of effects is challenging to investigate under traditional systems that include numerous disorders

and lack a robust hierarchical organization. Our review of validity evidence spotlighted many gaps in knowledge of specificity, and the HiTOP offers a framework to addressing them.

Clinical implications

The HiTOP approach has several implications for clinical care. First, HiTOP diagnosis is a profile of relevant psychopathology dimensions, and the patient is conceptualized in terms of deviations from the healthy range. Traditional diagnosis is de-emphasized, but can be assigned in parallel with HiTOP, such as to meet administrative requirements. Indeed, the consortium developed a cross-walk from HiTOP to ICD-10 codes (https://hitop.unt.edu/clinical-tools/billing-hitop).

At some point, scores have to be dichotomized to inform categorical clinical decisions. Of note, traditional diagnoses are dichotomous, but the cutoffs are not optimized for any particular clinical action, and reasons for their selection have not been explicit[18]. Optimal use requires development of multiple purpose-built cutoffs (e.g., one for initiating treatment with antipsychotics, another for hospitalization), as has been done in medicine for such dimensional variables as blood pressure, cholesterol, or weight[360]. This research has not been completed in psychiatry yet, but categories based on degree of statistical deviance (e.g., normal, mild, moderate and high severity) are already available for many measures.

Another consideration is that psychopathology dimensions may interact with each other and with other clinical parameters (e.g., age, medical comorbidities) in ways that change treatment indications and even meaning of scores, such as psychosis that emerges in late life in the context of dementia versus in young adulthood. Many of these interactions are well known, but systematic research is limited. The HiTOP model offers a framework for investigating this question.

Second, the HiTOP offers a hierarchical case conceptualization describing both general and specific features of psychopathology. For example, general dimensions (e.g., p factor) can identify high utilizers of care, thus helping to guide public health policy or policies of a given clinic[361]. In addition, a patient's standing on the thought disorder spectrum may suggest that antipsychotics are indicated. Moreover, on the specific level, an elevation on avolition symptoms may suggest social skills training. Importantly, a move to HiTOP case conceptualization does not negate prior research on traditional diagnoses. Information on treatment efficacy for disorders linked to the spectrum is retained and applied to people elevated on this dimension, although it will be important to verify treatment effects in HiTOP-based treatment studies.

Third, dimensional conceptualization of psychopathology emphasizes continuity with healthy functioning, which can facilitate communication with patients and family members, and help to reduce the stigma of psychopathology. Communication among providers may sometimes benefit from a simpler formulation than an exact score that a patient received on a dimension, and categorization can be applied based on the aforementioned cutoffs. For example, "moderately elevated detachment" could be used instead of listing the specific score.

A salient pragmatic concern is assessment burden on clinics. Many HiTOP assessments have been digitized, so that the questionnaire can be sent to patients for completion at home or in a waiting room, with results scored automatically and provided to clinicians in real time. Importantly, these measures do not aim to replace an intake interview, but to guide clinicians' interviewing, thus improving speed and comprehensiveness of an intake and subsequent monitoring, much like lab tests do in medicine.

FUTURE DIRECTIONS

The proposed HiTOP model of the psychosis superspectrum is based on extensive evidence. Nevertheless, further research is needed to verify assignment of mania and dissociation, as well as to incorporate other dimensions in the model (e.g., cognitive impairment and catatonia). The HiTOP is meant to include all empirical psychopathological entities, whether dimensional or categorical in nature. Only dimensions have been established empirically to date[18]. However, latent classes likely exist[362], so they need to be identified and added to the psychosis superspectrum alongside dimensions.

Research is also needed on optimal cutoffs for specific clinical decisions. Interactions among dimensions and with other clinical features need to be investigated systematically. It will be particularly important to verify and expand knowledge of treatment efficacy with dimensions as treatment targets. Finally, thought disorder and detachment spectra have been extensively validated, but gaps remain for a number of validators, such as childhood antecedents and biomarkers. Developmental processes, in particular, need more attention. This research can build on the strong base of knowledge and scientific framework provided by HiTOP.

CONCLUSIONS

The HiTOP offers a dimensional and hierarchical conceptualization of psychotic disorders that was derived strictly from data, free of political considerations. It has been extensively validated and already demonstrated considerable utility. Validated measures are available for spectra and their subdimensions for both symptoms and traits.

Further research is needed, but the model is ready for use by scientists and clinicians interested in psychotic disorders. Its application offers to address problems of heterogeneity, comorbidity and low reliability, providing more valid and predictive descriptions of patients.

APPENDIX

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