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Authors

Kotov, Roman

Carpenter, William

Cicero, David

et al.

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Psychosis Superspectrum II: Neurobiology, Treatment, and Implications

Roman Kotov[1], **William T. Carpenter**[2], **David C. Cicero**[3], **Christoph U. Correll**[4,5,6], **Elizabeth A. Martin**[7], **Jared W. Young**[8,9], **David H. Zald**[10], **Katherine G. Jonas**[1]

[1]Department of Psychiatry and Behavioral Health, Stony Brook University, Stony Brook, NY, USA

[2]Department of Psychiatry, University of Maryland, Baltimore, MD, USA

[3]Department of Psychology, University of North Texas, Denton, TX, USA

[4]The Zucker Hillside Hospital, Department of Psychiatry, Northwell Health, Glen Oaks, NY, USA

[5]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA

[6]Charité - Universitätsmedizin Berlin, Department of Child and Adolescent Psychiatry, Berlin, Germany, USA

[7]Department of Psychological Science, University of California, Irvine, Irvine, CA, USA

[8]Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

[9]Research Service, VA San Diego Healthcare System, San Diego, CA, USA

[10]Rutgers University, The State University of New Jersey, New Brunswick, NJ, USA

Abstract

Alternatives to traditional categorical diagnoses have been proposed to improve the validity and utility of psychiatric nosology. This paper continues the companion review of an alternative model, the psychosis superspectrum of the Hierarchical Taxonomy of Psychopathology (HiTOP). The superspectrum model aims to describe psychosis-related psychopathology according to data on distributions and associations among signs and symptoms. The superspectrum includes psychoticism and detachment spectra as well as narrow subdimensions within them. Auxiliary domains of cognitive deficit and functional impairment complete the psychopathology profile. The current paper reviews evidence on this model from neurobiology, treatment response, clinical utility, and measure development. Neurobiology research suggests that psychopathology included in the superspectrum shows similar patterns of neural alterations. Treatment response often mirrors the hierarchy of the superspectrum with some treatments being efficacious for psychoticism, others for detachment, and others for a specific subdimension. Compared to traditional diagnostic systems, the quantitative nosology shows an approximately 2-fold increase in reliability, explanatory power, and prognostic accuracy. Clinicians consistently report that the quantitative nosology has more utility than traditional diagnoses, but studies of patients with frank psychosis are currently lacking. Validated measures are available to implement the superspectrum model in practice. The dimensional conceptualization of psychosis-related psychopathology has implications for research, clinical practice, and public health programs. For example, it encourages use of the cohort study design (rather than case-control), transdiagnostic treatment strategies, and

selective prevention based on subclinical symptoms. These approaches are already used in the field, and the superspectrum provides further impetus and guidance for their implementation. Existing knowledge on this model is substantial, but significant gaps remain. We identify outstanding questions and propose testable hypotheses to guide further research. Overall, we predict that the more informative, reliable, and valid characterization of psychopathology offered by the superspectrum model will facilitate progress in research and clinical care.

The task of a nosology is to guide research and clinical practice. However, traditional diagnostic manuals have significant limitations in both, which led to development of alternative models.[1] This article is the second of two papers reviewing evidence on an alternative, the Hierarchical Taxonomy Of Psychopathology (HiTOP) model of psychosis-related psychopathology (represented in diagnostic manuals by psychotic, bipolar, dissociative, schizotypal personality, paranoid personality, schizoid personality, and avoidant personality disorders). The first paper described the model, a set of hierarchically-organized dimensions: the overarching psychosis superspectrum, the psychoticism and detachment spectra within it, and narrow constructs at the lowest level—six symptom components (e.g., disorganization, avolition) and eight maladaptive traits (e.g., unusual beliefs, romantic disinterest).[1] Another term for “psychoticism” is “thought disorder,” but it includes all positive symptoms. The paper also outlined relevant dimensions of cognition and real-world functioning, two auxiliary domains that are not part of the superspectrum but are integral to a thorough assessment. The first paper reviewed evidence from nosology, etiology (genetic and environmental), and lifespan development regarding the validity of this model. The current paper discusses evidence from neurobiology, treatment response, utility, and measure development, as well as practical implications and outstanding research questions. It integrates evidence across studies that assessed symptoms (positive and negative), schizotypal traits, and personality pathology dimensions, aligning them to a common terminology (e.g., psychoticism and detachment).

Neurobiological processes linked to the superspectrum

Studies that assess psychopathology dimensionally provide the most direct data on neural substrates of the superspectrum. Such research is increasing but still rare. Fortunately, certain inferences can be made from traditional case-control studies about neural underpinnings of the superspectrum based on commonalities among disorders linked to it. We review this evidence next, emphasizing meta-analytic and large-scale studies. We also consider key transdiagnostic and normative studies that directly address neural correlates of the superspectrum.

Grey matter.

Mega- and meta-analyses indicate that cortical thinning is widespread in schizophrenia, schizoaffective disorder, and bipolar disorder.[2,3] Also, these disorders and clinical high risk for psychosis (CHR-P) are associated with reduced volume in several subcortical regions, such as hippocampus.[2,4–7] A critical question is the specificity of these reductions given that at least in youth, broad reductions in cortical thickness or volume are associated with the general p-factor of psychopathology.[8–11] Moreover, hippocampal and regional cortical

volume reductions are seen in multiple disorders outside of the psychosis superspectrum and in some cases are similar in size to reductions found in psychotic disorder.[3,12] However, the reduction in cortical thickness observed in the psychosis superspectrum is notable in its expansiveness, spanning all frontal and temporal gyri. Rather than emphasizing individual brain regions, recent analyses have focused on the overall pattern of volumetric and morphometric alterations across brain regions. For instance, mega-analysis of data from the ENIGMA consortium found that subcortical volume and cortical thickness profiles of schizophrenia and bipolar disorder are very similar to each other (r = .81) but are largely dissimilar from profiles of internalizing (major depressive disorder, obsessive-compulsive disorder), externalizing (attention-deficit/hyperactivity disorder), and neurodevelopmental (autism spectrum disorder) psychopathology.[13] A recent meta-analysis of structural alterations in 14 psychiatric conditions confirmed that schizophrenia, schizoaffective disorder, bipolar disorder with psychosis, unspecified psychotic disorder, and CHR-P have similar regional profiles, and they are distinct from profiles of internalizing disorders, ADHD, and autism.[3] An important caveat is that bipolar disorder without psychosis had a different profile from psychotic disorders.[3] Overall, this evidence indicates that disorders linked to the psychosis superspectrum show similar alterations in grey matter, and this profile is distinct from profiles of other superspectra, so it cannot be fully explained by the p-factor.

Dimensional phenotyping in studies of patients has largely focused on positive and negative symptoms. While this captures only one aspect of psychoticism and detachment spectra, such data provide strong evidence for distinctions in the neural correlates of these dimensions. Specifically, detachment symptoms are associated with widespread cortical thinning,[14] whereas psychoticism symptoms are related to a more selective thinning within lateral temporal, ventromedial frontal, and cingulate areas.[15] Also, detachment symptoms have been associated with volume reductions in multiple brains regions such as the medial orbitofrontal and insular regions, particularly in samples with more chronic illness.[16–18]

Structural connectivity.

Meta- and mega-analyses indicate the presence of widespread reductions in the integrity of white matter tracts in schizophrenia, schizoaffective disorder, and bipolar disorders.[19–25] These declines are particularly pronounced in certain tracts including the fornix, cingulum, posterior thalamic radiation, and portions of the corpus callosum. While reductions in the integrity of white matter are not unique to the psychosis superspectrum,[26,27] disorders linked to the superspectrum show particularly marked decrements. A mega-analysis of white matter microstructure found that the pattern of alterations in schizophrenia and bipolar disorder are very similar to each other (r = .72) and less similar to regional profiles of internalizing disorders.[19] Some analyses have suggested that the broad decrements in white matter integrity are specific to detachment symptoms,[28,29] although results have been variable in terms of strength and specificity of this association.[30,31]

Functional connectivity.

Altered resting-state functional connectivity has been repeatedly observed in schizophrenia, schizoaffective disorder, bipolar disorder, and CHR-P.[32–36] Alterations have been especially

prominent within the default mode, frontoparietal, cingulo-opercular/ salience, ventral attention and thalamocortical networks, typically manifesting in reduced within network connectivity and decreased segregation between networks. These alterations are not restricted to the psychosis superspectrum, and some may be correlates of the broader p-factor.[32,37–40] However, several observed effects are more prominent in disorders linked to the superspectrum than in non-psychotic disorders.[32,37,41]

Many functional connectivity findings align with theories of schizophrenia pathophysiology. For example, abnormalities in thalamo-cortical networks were specified in the cognitive dysmetria model.[36,42] Altered salience, central executive, and default mode networks were anticipated in the triple-network saliency model of schizophrenia.[43] Given that alterations in these networks are found across disorders linked to the superspectrum, cognitive dysmetria and triple-network saliency theories may be relevant to the entire superspectrum.

The extent to which functional connectivity selectively relates to the psychoticism or detachment spectra is an active area of exploration. A meta-analysis found that greater detachment symptoms are associated with lower default mode connectivity.[35] This effect was confirmed in a large transdiagnostic study,[33] although these relationships may be affected by methodology for characterizing connectivity or subnetworks.[32] Examining segregation between networks in the CHR-P population, a recent meta-analysis found that decreased segregation between default mode, salience, and central executive networks was associated with detachment symptoms but not psychoticism symptoms.[44] By contrast, large community studies of youths have found that psychoticism symptoms are associated with reduced segregation between networks.[45,46] Further work with attention to differences in samples and phenotyping are needed to clarify these results.

Continuity across severity.

Neural abnormalities linked to HiTOP dimensions are expected to manifest across levels of severity. Studies of grey matter are partially consistent with this pattern. In normative samples, traits (i.e., schizotypy) and subclinical symptoms (i.e., psychotic-like experiences) were linked to temporal cortical grey matter reductions also observed in psychotic disorders, but did not clearly show other morphologic alterations found in clinical samples.[47–49] Likewise, subthreshold psychoticism symptoms were related to some structural connectivity disruptions common in psychotic disorders.[48,50,51] Moreover, the largest study to date reported that distressing psychotic-like experiences are associated with global decrements in white matter integrity.[52] Finally, traits and subclinical symptoms are associated with functional connectivity alterations also found in psychotic disorders.[49,53–55] These initial studies are encouraging, but the hypothesis of continuity across levels of severity requires further investigation.

Neurophysiology.

Inhibitory processes have been studied across the superspectrum using antisaccade eye movement and sensory gating/P50. Abnormalities in these markers were found in schizophrenia, schizoaffective disorder, and bipolar disorder.[56–60] Antisaccade eye movement deficits are related to superspectrum traits, showing similar associations with

psychoticism and detachment.[61] In contrast, sensory gating deficits are consistently linked to cognitive impairment rather than symptoms.[62]

Pre-attentive stimulus processing and sensory memory have been studied using mismatch negativity (MMN).[63] MMN is an event-related potential (ERP) linked to glutamatergic neurotransmission.[64] Blunted MMN has been found in schizophrenia, schizoaffective disorder, bipolar disorder, and CHR-P.[65–68] Reduced MMN is associated with psychoticism and detachment, assessed as traits or as symptoms.[69,70] MMN is also correlated with cognitive and real-world functioning.[62,70] Overall, blunted MMN appears to be a general marker of the superspectrum.

Attentional processes can be indexed by the P300, an ERP related to dopaminergic, noradrenergic, and glutamatergic activity.[71,72] Auditory P300 deficits have been found in schizophrenia, schizoaffective disorder, bipolar disorder, and CHR-P.[73–77] P300 has two subcomponents, P3a (marker of automatic orientation of attention) and P3b (stimulus categorization and response). P3a is largely unrelated to symptoms.[70,75] The P3b deficit has been linked to psychoticism symptoms,[75] but its relationship to detachment is unclear.

Performance monitoring has been investigated using error-related negativity (ERN).[78,79] This ERP is linked to activity of the dorsal anterior cingulate cortex.[80,81] Blunted ERN has been found in schizophrenia, schizoaffective disorder, and bipolar disorder.[82,83] Reduced ERN has been linked to detachment symptoms, cognitive deficits, and functional impairment.[84]

Some of the aforementioned neurophysiologic alterations are specific to the psychosis superspectrum relative to other domains of psychopathology. MMN deficits are larger in psychotic disorders[67,85] than in internalizing and externalizing conditions.[86,87] ERN is usually enhanced in internalizing disorders, modestly reduced in externalizing disorders, and shows the greatest reductions in psychotic disorders.[82,88,89] In contrast, P300 abnormalities may not be specific to the superspectrum, as major depression and substance use disorders exhibit deficits of similar magnitude.[74,75,90,91] Too few studies have considered antisaccade eye movement and sensory gating across spectra to draw conclusions regarding specificity.

Overall, psychosis-related psychopathology is linked to common neural alterations. Some abnormalities appear to be associated with the general superspectrum (e.g., cortical thickness pattern, MMN, and antisaccade eye movement deficits), whereas emerging evidence suggests others may be related to detachment (e.g., widespread white matter dysconnectivity), or cognitive and functional impairment (e.g., sensory gating deficit).

Animal models of the superspectrum

Definitive studies of neural mechanisms underpinning the superspectrum require manipulations that are most feasible in animals. A major barrier to cross-species research is that psychotic disorders cannot be fully recreated in animals.[92] Instead, animal researchers have been able to recreate specific behavioral abnormalities using manipulations theoretically relevant to etiology or pathophysiology of psychosis.[92]

This presents a two-fold challenge to cross-species translation and the superspectrum model helps to address both. First, modeled behavioral features are more specific than traditional disorders. In contrast, they usually map well on lower-order dimensions of the superspectrum (see Table 1). Some constructs are difficult and probably impossible to recreate in animal behavior, such as many subdimensions of psychoticism (e.g., fantasy proneness, unusual beliefs). However, most constructs in domains of detachment, cognition, and functional impairment are readily testable in animals (Table 1). Second, animal models typically are not specific to one psychiatric disorder. Manipulations used to develop models often have general effects. For example, polymorphisms in Sp4 and DISC1 genes that some models are based on have been linked to bipolar disorder, schizophrenia, and depression.[93–95] Moreover, many modeled behaviors are relevant to multiple conditions.[96] Manipulations and their behavioral consequences usually align better with the psychosis superspectrum (or spectra within it) than traditional disorders.[1] Accordingly, the superspectrum model can help to advance cross-species research by offering targets for translation that can be modeled with greater fidelity than traditional disorders.

The Research Domain Criteria (RDoC) initiative offers another approach to cross-species translation. It is a research framework proposed by the National Institute of Mental Health for clinical studies.[97] The RDoC identified basic biobehavioral functions relevant to psychopathology that can be assessed across multiple units of analysis, including genes, molecules, cells, and behavior.[98] HiTOP and RDoC are similar in adopting the dimensional approach to address shortcomings of traditional diagnoses, and there are parallels among constructs included in these models.[99] However, there are also significant differences. RDoC does not explicitly include clinical symptoms, focusing instead on more fundamental processes (e.g., perception, social communication). Hence, RDoC is a research framework rather than a clinical taxonomy.[100] Conversely, HiTOP is focused on symptoms and agnostic about their biologic substrates.

HiTOP can complement RDoC with clinical targets for validating RDoC measures to ensure their clinical relevance (Figure 1). This would facilitate clinical application of RDoC by mapping its constructs to symptoms that bring patients to treatment. Conversely, RDoC can inform revision of HiTOP. Some RDoC constructs become psychopathology in their extremes (e.g., extremely low RDoC Initiation of Motor Actions manifests as apathy or RDoC Agency as delusions of control) and should be included in HiTOP to achieve a comprehensive taxonomy. Moreover, connections with RDoC help to explicate biological processes underpinning HiTOP constructs. Ultimately, research on linkages between RDoC and HiTOP can lead to development of a unified nosology that encompasses both pathophysiology and precise clinical descriptions.[101]

With regard to translation, RDoC approach enables the development of cross-species tests of basic biobehavioral functions, particularly translating between healthy participants and control animals (Figure 1). HiTOP helps to identify manipulations (e.g., genetic and environmental factors)[1] implicated in the psychopathology constructs that can be recreated in animals. Hence, HiTOP and RDoC can jointly guide development of animal models by combining manipulations selected in research on HiTOP with cross-species tasks (i.e., behavioral outcomes) developed using the RDoC approach. Such animal models are

expected to help elucidate etiology and pathophysiology of the psychosis superspectrum and test novel transdiagnostic therapeutics.

Treatment efficacy in the superspectrum

Pharmacologic interventions.

The psychoticism spectrum shows a common response to dopamine receptor blockers (also called “antipsychotics”), including dopamine D2 receptor partial agonists. Dopamine blockers are efficacious across psychotic disorders,[102–107] supporting the transdiagnostic approach to treatment. These medications show medium to large effect sizes for both reality distortion and disorganization. Antipsychotics are also efficacious in treating and preventing mania.[108–110] With regard to specificity some, but not all, dopamine blockers also have antidepressant activity. This pertains to both bipolar and unipolar depression,[111,112] in monotherapy or augmentation of mood stabilizers and antidepressants. The antidepressant action likely is related to serotonergic or partial dopamine agonist activity. Furthermore, dopamine blockers are effective in treating aggression and agitation in autism and dementia.[113,114] Overall, dopamine blockers show highest efficacy for psychoticism but have an effect on certain internalizing symptoms as well.

Consistent with the dimensional model, preliminary evidence suggests that dopamine blockers may be beneficial across the spectrum of severity and can reduce psychoticism in patients who do not have frank psychosis.[115] Some studies also found that antipsychotics can reduce psychoticism (risk of transition) in CHR-P.[116,117] However, consistency of this evidence is limited, likely due to the small number and size of available studies. Both dopamine blockers and placebo significantly improved psychoticism symptoms, so larger samples are needed to isolate treatment effects. Although several other medication classes have been reported to improve psychoticism symptoms, the evidence is limited by small or poor quality studies.[118]

In contrast, the detachment spectrum shows weak response to dopamine blockers, and observed benefits may be limited to negative symptoms that are secondary to psychosis or depression.[119,120] Some partial D3 or D2 agonists may be exceptions,[121,122] but their effects on detachment are modest. Antidepressants produce small improvement in detachment symptoms,[123,124] but they do not reduce psychoticism in high quality studies[118] and can exacerbate mania.[125] Other medication classes for detachment are still in experimental stages[126] or need rigorous studies.[118] Tentative evidence suggests that neuromodulation techniques providing stimulation to specific neural networks can improve negative symptoms,[127,128] but this research is still limited by heterogenous results, short-term follow-ups, and low study quality.

Glutamate and ion channel modulators, such as antiepileptic agents and lithium, are efficacious for mania.[108,109,129] When administered in combination with antipsychotics, some antiepileptic agents can improve psychoticism and detachment, but lithium has not shown efficacy for either.[118] This suggests that lithium acts on the lower-order construct, mania, rather than the general spectra.

No medication is approved for treatment of cognitive dysfunction in psychotic disorders to-date. Existing dopamine blockers may improve cognitive impairment secondary to psychoticism symptoms, but excessive dopamine blockade can worsen cognition.[130] Overall, benefits of dopamine blockers on cognition are small.[131,132] Antidepressants have no or very small beneficial effect on cognition.[133] Evidence on whether other medication classes can reduce cognitive dysfunction more than placebo is either insufficient[118] or still in experimental stages.[126]

Real-world functioning in psychotic disorders improves with dopamine blockers,[134] but mainly due to reduction of psychoticism symptoms. Overall, rates of recovery—defined as symptom remission and adequate functioning—have remained very low across 50 years of research,[135,136] which is attributed to elevated detachment and cognitive deficits that are not adequately addressable by existing pharmacologic interventions.[126,137,138]

As novel medications become available that do not block dopamine receptors, it may become possible to simultaneously improve psychoticism and detachment.[139,140] Examples of such agents are muscarinic agonists, including the M1/M4 muscarinic agonist KarXT (i.e., xanomeline combined with the peripheral anticholinergic trospium),[141–143] M4 muscarinic positive allosteric modulator emraclidine,[144] trace-amine associated receptor (TAAR)1/5HT1A agonist ulotaront,[145,146] and, possibly, the 5HT2A and 5HT2C antagonist/inverse agonist pimavanserin.[147,148] Additional mechanisms of action are currently being investigated in phase 2 and phase 3 study programs—either as monotherapy or augmentation of dopamine blockers—to treat psychoticism, detachment, cognitive deficits, or functional impairment in schizophrenia.[126]

Behavioral interventions.

The psychoticism spectrum shows a common response to two psychotherapies. Cognitive behavioral therapy (CBT) improves psychoticism symptoms compared to treatment-as-usual and active comparisons, with the reduction persisting post-treatment.[149,150] Moreover, CBT is effective in preventing future exacerbations of these symptoms.[151] CBT also prevents transition from CHR-P to frank psychosis.[152] Likewise, Metacognitive Training for Psychosis improves psychoticism symptoms, and this reduction endures at least one year post-treatment.[153] However, all of these effects are modest.

The detachment spectrum shows a common response to CBT, which is efficacious across psychotic disorders compared to treatment-as-usual, and its benefits persist at follow-up.[150,154] Other psychotherapies are specific to detachment. Social skills training improves both detachment symptoms[150,154,155] and detachment traits.[156] It also reduces transition from schizotypal personality disorder to psychotic disorder.[157] Cognitive remediation reduces detachment symptoms compared to treatment-as-usual with benefits persisting post-treatment.[150] Multiple other interventions produce modest improvements in detachment symptoms at the end of treatment, but it is uncertain if these benefits endure.[150]

Cognitive dysfunction shows small but reliable response to cognitive remediation that persists post-treatment.[150,158,159] Cognitive remediation also improves real-world functioning, although the effect is small.[158] Likewise, CBT, Metacognitive Training for

Psychosis, and mindfulness-based therapies reduce functional impairment, with small to moderate effect sizes.[120,153]

With regard to specificity relative to other psychopathology, CBT principles have established efficacy for many forms of psychopathology.[160] However, psychosis spectrum research primarily studied CBT for psychosis (CBTp), which specifically focuses on psychoticism and detachment symptoms, making it a distinct treatment.[149] Cognitive remediation was found to improve cognition across diagnostic groups, but data on treatment's efficacy for internalizing and externalizing symptoms are equivocal.[161] Metacognitive Training targets both general mechanisms of thinking and biases specific to reality distortion, so its applications focused primarily on psychotic disorders. Recently this treatment has been adapted for internalizing psychopathology, but the number of controlled trials is too limited to compare efficacy between internalizing and reality distortion.[162] Likewise, social skills training has not been sufficiently studied outside the psychosis superspectrum for clear inference about its relative efficacy.[163,164] Mindfulness-based therapies are efficacious for various forms of psychopathology.[165] Benefits may be particularly large for psychotic disorders, but the small number of studies in this population preclude a definite conclusion.[165]

In summary, dopamine blockers are efficacious for psychoticism overall, and benefits are observed across disorders and levels of severity. In contrast, dopamine blockers offer only small benefits (likely secondary to reduction in psychoticism) for detachment, cognition, and real-world impairment. Dopamine blockers also can ameliorate some internalizing symptoms, so their effects are not limited to psychoticism. Antidepressants achieve a small improvement in detachment, but not psychoticism, cognition, or functioning. No other pharmacologic intervention is established as efficacious for any of these constructs to-date. Behavioral interventions can address these gaps. CBT is efficacious for detachment and functional impairment, as well as psychoticism. Cognitive remediation improves cognition, detachment, and functioning. Metacognitive Training for Psychosis has benefits for functioning and psychoticism. Social skills training is efficacious for detachment, while mindfulness-based therapies are efficacious for functional impairment. These therapies are based on therapeutic principles that operate across psychopathology, but the treatments have been adapted to the superspectrum. Existing data are insufficient to determine impact of this adaptation on specificity of efficacy. Much less is known about treatment for lower-order dimensions, but some therapeutics show specific effects. For example, lithium is efficacious for mania rather than psychoticism or detachment, and social skills training may be particularly efficacious for avolition—a component of detachment.[166]

Utility of the superspectrum

Utility of a nosology includes reliability, validity, and clinical utility. The companion paper introduces challenges to reliability of traditional diagnoses.[1] Both the present paper and the companion discuss validity of the psychosis superspectrum model itself. In this section, we directly compare the superspectrum and traditional models on reliability, validity, and clinical utility.

Reliability.

Reliability is a prerequisite for utility, as an unreliable diagnosis cannot convey useful information. Despite decades of efforts to improve diagnostic reliability, the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)[167] field trials found only a mediocre agreement between diagnosticians, with an inter-rater reliability (kappa coefficient) of .40 to .56 for schizophrenia, schizoaffective disorder, and bipolar disorders.[168] The temporal stability of psychotic disorder diagnoses is also inadequate, with kappa ranging .13 to .65.[169] It appears that reliability of traditional systems has reached its ceiling, limited by the fundamental mismatch between categorical diagnoses and the continuous nature of psychopathology.[170] Indeed, the DSM-5 field trials found that dimensional ratings of psychotic symptoms are more reliable than the diagnostic categories, increasing test-retest correlations to .72 - .79.[171]

Studies of the broader detachment and psychoticism spectra also found high reliability, with 2-week test-retest correlations ranging .81 to .89.[172–174] Likewise, meta-analytic estimates of reliability are .81 for psychoticism (thought disorder) and .85 for detachment (pathological introversion) pooled across numerous interview-based and self-report measures.[175] Compared to traditional systems, psychoticism and detachment show much higher 2-week test-retest reliability (.88 and .89, respectively) than relevant personality disorder diagnoses: paranoid, schizoid, schizotypal, and avoidant (range .44 to .63).[172] Overall, these findings indicate that the superspectrum model provides a reliable description of psychopathology and improves reliability over DSM-5 diagnoses nearly 2-fold.

Validity.

Validity of a nosology includes ability to explain and predict external validators. A meta-analysis found greater validity for dimensional than categorical operationalizations of psychoticism (thought disorder) and detachment (pathological introversion).[175] For psychoticism, 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, this meta-analysis was based primarily on non-psychotic disorders (e.g., personality pathology).

Four studies compared the validity of quantitative and traditional nosologies in patients with psychotic disorders (Table 2). These studies operationalized the quantitative nosology with a set of symptom dimensions relevant to psychosis. Three studies evaluated concurrent associations with neurophysiologic biotypes, cognitive functioning, real-world functioning, and service utilization.[176–178] The quantitative model was superior to traditional diagnoses in every case, providing a 3.5-fold increase in explanatory power on average. One study evaluated prediction of outcomes 20 years later, including remission, recovery, physical health, real-world functioning, cognitive functioning, and neurophysiologic deficits.[179] The quantitative model was superior to traditional diagnoses in 12 out of 13 comparisons (cognitive functioning was the exception), with a 2.3-fold increase in prognostic power on average.

Several other studies did not focus on the superspectrum model, but examined HiTOP overall and found that it offers greater validity than the DSM.[180] For example, a 10-year follow-up of personality disorders—including schizotypal personality disorder—examined several outcomes (e.g., illness severity, suicide attempts, social functioning, medication use) and found prognostic power (R^2) of 0.25 for dimensions versus 0.12 for diagnoses.[181] In sum, existing research indicates that the psychosis superspectrum model more than doubles explanatory and prognostic power compared to the DSM, thus increasing the value of diagnosis for researchers and clinicians.

Clinical Utility.

Clinical utility of a nosology (or a given diagnostic feature) is defined as its ability to facilitate implementation, conceptualization, communication, treatment selection/planning, and outcome improvement.[182,183] Traditional diagnostic manuals have major limitations in clinical utility. A survey of 1,764 clinicians revealed that 49.8% often or routinely make diagnosis without referring to the diagnostic criteria.[184] Clinicians reported that diagnosis provides limited guidance in treatment selection and prognostication, and is used primarily for billing, training, and communication among professionals.[184] These findings are consistent with the extensive off-label prescribing in psychiatry. For instance, up to 75% of all antipsychotic prescriptions to adults are off-label.[185] This pattern fits with the evidence that traditional diagnoses align poorly with psychotropic drug action and optimal prescribing practices.[186]

Other clinician surveys directly compared quantitative and traditional systems. Many studies focused on personality pathology and consistently found that clinicians favor the quantitative nosology, especially in treatment formulation and communication with patients.[187–189] This pattern was observed for psychiatrists as well as other providers, contradicting a common assumption that psychiatrists prefer categories.[190] Similar findings are emerging for other forms of psychopathology. In the DSM-5 field trials, dimensional measures included in the manual were rated by 80% of clinicians as moderately to extremely helpful.[191] In another study, 143 practicing clinicians reviewed a clinical vignette (randomly selected from a set), used both HiTOP and DSM-5 to describe the case, and then rated the clinical utility of each system.[192] HiTOP was rated as superior to DSM-5 in the ease of applying the system, comprehensively describing psychopathology, describing functioning, formulating treatment, and communicating to patient, but the systems had equal utility for communicating with other clinicians. Overall, substantial evidence indicates that HiTOP can improve the clinical utility of diagnosis. However, further research is needed in populations with frank psychosis, individual features of HiTOP rather than the whole model, and the impact of alternative diagnostic systems on objective criteria such as treatment outcomes.

The evidence of clinical acceptability is consistent with data that practitioners rely on presenting signs and symptoms more than on traditional diagnoses.[193] This approach is part of an established practice of dimensional, symptom-oriented and personality-informed case conceptualization.[194] HiTOP seeks to formalize and improve this practice by offering clinicians a rigorous framework and validated assessments of relevant dimensions. HiTOP also builds on the practice of using dimensional measures in psychiatric care. Rating

scales for psychosis and related symptoms have been part of clinical practice and research for decades, starting with the Brief Psychiatric Rating Scale.[195] These dimensional measures have proven clinical acceptability and are required in clinical trials for psychotic disorders.[196] We summarize the most relevant instruments next.

Measurement of the superspectrum

Various instruments for assessment of the superspectrum have been developed.[197] Some measure symptom dimensions and others assess traits. Supplementary Table 1 maps these instruments onto superspectrum constructs.

Both the DSM-5 and International Classification of Diseases, 11th revision (ICD-11)[198] include dimensional ratings of symptoms relevant to the superspectrum (e.g., negative symptoms).[199,200] Although an improvement over categorical diagnoses, reliability of these individual ratings is limited.[171] Scales composed of multiple ratings offer substantially higher reliability.

Several widely-used symptom interviews include such scales. Interview measures of CHR-P provide a precise assessment of the subclinical range,[201,202] whereas symptom rating scales focus on the clinical range. Validated self-report measures of the superspectrum are also available. Trait measures include scales developed to assess either schizotypy (trait vulnerabilities to psychosis)[203,204] or personality pathology. Symptoms can be assessed by the Achenbach System of Empirically Based Assessment,[205] an extensively-validated suit of scales for children and adults that includes relevant dimensions.

However, no existing instrument addresses all dimensions of the superspectrum, and a battery of measures is needed. The Clinical Translation Workgroup of the HiTOP consortium developed such a battery, the HiTOP Digital Assessment and Tracker (HiTOP-DAT).[206] It assesses dimensions with the superspectrum, other HiTOP spectra, and functional impairment. The scales were selected from seven open-source self-report inventories, based on evidence of reliability, validity, and sound normative data.

To comprehensively assess HiTOP with a single instrument, the Measures Development Workgroup of the HiTOP consortium is constructing the HiTOP Self-Report (HiTOP-SR) and accompanying interview (iHiTOP).[207] These dedicated measures of HiTOP will provide a thorough assessment of the psychosis superspectrum. These efforts began with 19 candidate constructs, and the workgroup has been testing them to identify a set of non-redundant and valid subdimensions.[208]

The auxiliary domains can be assessed with a variety of instruments. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery[209] is the most comprehensive assessment of cognition and was developed specifically for psychotic disorders. It lacks a measure of verbal comprehension, but can be supplemented by the Vocabulary, Similarities, or Information subtest of intelligence batteries.[210] Real-world functioning can be thoroughly assessed by the World Health Organization Disability Assessment Schedule (WHODAS 2.0),[211] a companion measure to the ICD and DSM-5. The WHODAS 2.0 can be administered either as a questionnaire

or an interview. It has been validated in samples with elevated psychoticism or psychotic disorders.[212,213]

All aforementioned measures are cross-sectional, which can provide a general sense of illness course, such as by comparing elevations on maladaptive traits (persistent problems) and symptoms (current state). However, specific course patterns offer rich information with implications for treatment and prognosis.[1] Existing course descriptors (e.g., age of onset, remission) are heuristic, but research is ongoing to identify empirically-sound course features.[214] Once these features are added to the model, HiTOP measure development will need to address the challenge of assessing such features accurately based on retrospective reports or mobile monitoring.

Implications for research

The superspectrum model has multiple conceptual implications for research. First, it conceptualizes schizophrenia and related disorders not as distinct groups, but as elevations on fundamental dimensions. Studies of these dimensions can be more informative, offering greater reliability and statistical power.[172,179,215] In particular, research that focuses on reality distortion symptoms overlooks the persistent psychoticism traits. These traits may be less severe but can show stronger associations with genetic and neurobiologic mechanisms owing to their temporal stability.[216,217] Second, the detachment spectrum is equally important but poorly understood, as the majority of existing studies defined cases based on reality distortion, in keeping with traditional diagnoses. Elevated detachment can occur without history of psychosis, but these cases are invisible to studies based on DSM-5 and ICD-11, and existing data on detachment are usually confounded with reality distortion by design. Third, the model suggests that the etiology and pathophysiology of psychosis is not unique to a given disorder, rather these processes occur across the general population in different degrees and are often common across psychotic disorders. Fourth, nevertheless, some pathologic processes are associated with specific subdimensions (e.g., inexpressivity).[166,218] The hierarchical arrangement of dimensions allows studies to determine whether a given effect is linked to the superspectrum or a lower-order dimension.[219] Fifth, diagnostic manuals address presumed interactions between psychopathology constructs by specifying new groups (e.g., schizoaffective disorder to capture the co-occurrence of reality distortion and depression or mania, as this may portend better outcome). The dimensional approach tests these hypotheses rigorously as statistical interactions between continuous scores. Overall, the superspectrum model suggests that scientific progress can be accelerated by studying dimensions, both traits and symptoms, in samples drawn from the general or heterogeneous patient populations. It is particularly important to study detachment regardless of psychosis and examine both lower-order and higher-order dimensions.

The model also has implications for study design. Case-control design is common in research on psychotic disorders, but when applied to a continuous construct it creates two problems.[220,221] First, it excludes a large portion of the general population who are not clear cases or controls because of subthreshold symptoms. Many studies also exclude cases who have significant comorbidities. Consequently, this research is not representative of

either community or patient populations. Second, it is typical to use different recruitment strategies (e.g., clinical settings vs. community) for cases vs. controls. This difference introduces many confounds, as treatment-seeking is associated with higher rates of distress, impairment, comorbidities (mental and physical), and exposure to medication. Hence, it is often uncertain to what extent findings of case-control studies reflect these confounds. The superspectrum model encourages studies in community samples or unselected patient samples, potentially oversampling for high scores on the target dimension to ensure sufficient sample size across levels of severity. Inclusion criteria may be very broad, as long as the participant can provide valid data on study assessments. Comorbidities and other confounds can be managed statistically, provided an adequate sample size. In fact, it is more informative to address comorbidities through assessment rather than exclusion, as then specificity of effects to target psychopathology versus comorbidities can be tested directly. This strategy can be cost-effective, as cases with first-episode psychosis or CHR-P are slow and costly to recruit, whereas many more people experience moderate psychoticism symptoms.

The superspectrum model also has implications for measurement. The model characterizes psychopathology as a dimensional profile. A study can focus on a subset of dimensions (e.g., the higher-order spectra) or even a single construct. However, the assessment is most informative when the profile is as comprehensive as possible to investigate specificity of observed effects. Also, it is useful to assess both symptoms and maladaptive traits, as they capture the superspectrum in different timeframes. In many cases, brief self-administered instruments can be used to minimize assessment burden. In contrast, disorder ascertainment usually requires a diagnostic interview administered by a professional, which limits its scalability. Dimensional assessments do not have complex criteria for symptom duration, sequence, and hierarchical exclusions inherent in traditional diagnoses, which allows construction of valid self-report instruments for all superspectrum subdimensions (Supplementary Table 1). These self-reports are scalable to populations. Interview measures can be used in settings where self-report may be inaccurate (e.g., acute care) or to confirm scores after selecting study sample on a self-report screener. The Box illustrates these implications with three hypothetical studies.

For animal modeling, the psychosis superspectrum provides a number of constructs that can be examined in other species (Table 1). These constructs are more specific than traditional disorders, which is consistent with the recognition in animal modeling that psychiatric disorders cannot be fully recreated in animals, only certain behavioral features.[92] When non-specific links are observed between animal models and psychopathology, these effects can be understood as reflecting general spectra or superspectra rather than narrow constructs. Moreover, translation of animal findings to humans can benefit from transdiagnostic study designs, bringing human and animal studies in closer alignment for comparable testing across species. For example, rodent research has shown that κ-opioid receptor antagonists improve deficient reward processing.[222] Next, a randomized controlled trial (RCT) selected participants based on elevated anhedonia trait across diagnoses and found that κ-opioid antagonist improves deficient reward processing in humans.[223] This example illustrates both the potential of transdiagnostic research and the synergy between RDoC and HiTOP, with RDoC construct reward processing linking to trait anhedonia in HiTOP.

Implications for clinical practice

The dimensional approach has a long history of successful use in case conceptualization and treatment in child psychiatry and clinical psychology.[205,224] Neuropsychological and intelligence profiles have been used clinically in neurology and psychiatry for decades.[225] Medical laboratory tests that provide continuous scores are indispensable in medicine. The superspectrum model extends these practices to behavioral profiling of patients with psychosis-related problems.

A HiTOP diagnosis is a patient's profile on psychopathology dimensions (e.g., Figure 1).[226] In the profile, spectra describe the main difficulties the patient experiences, whereas lower-order dimensions detail specific issues. Maladaptive traits capture persistent problems, and symptom components describe the current state. To guide decision-making, clinical ranges are specified on each dimension. Currently, ranges are defined 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.[226] Work is underway to specify ranges for particular clinical actions, following examples of internal medicine (e.g., hypertension stages).[227]

HiTOP can be implemented clinically using self-report and interview measures described earlier. An efficient option is the fully-automated HiTOP-DAT that patients complete at home or in the waiting room. A monitoring version of HiTOP-DAT can be used to track treatment systematically by sending relevant scales to the patient on a desired schedule. The Clinical Translation Workgroup has developed HiTOP-DAT training materials for providers, including a crosswalk to translate HiTOP elevations into ICD-10-CM codes that meet administrative requirements (https://hitop.unt.edu/introduction). HiTOP-DAT is a self-report instrument, and the clinician would usually follow-up on HiTOP-DAT elevations when interviewing the patient. Moreover, a HiTOP profile is only one element of a psychiatric evaluation. Clinicians integrate the profile with other information (e.g., medical comorbidities, stressors, treatment history) to develop a case formulation. HiTOP contributes to this process a quantified, detailed, and systematic description of psychopathology. HiTOP does not attempt to identify etiology of psychosis, as it is often unclear, but clinicians are encouraged to consider etiology and specify it when possible.

The superspectrum model has four implications for treatment planning. First, clinicians can target either the general psychoticism or detachment, where treatment can affect multiple problems simultaneously,[228] or the lower-order dimensions, when a specific behavior is particularly significant (e.g., mania) or requires a specialized intervention (e.g., social skills training for avolition). Second, dimensional case formulation can inform selection of intervention appropriate for the level of severity (e.g., outpatient treatment at moderate severity, partial hospitalization program at higher severity). Multiple ranges can be specified on a dimension, each indicating a particular action, whereas traditional diagnosis provides only one threshold. Third, traits provide valuable prognostic information and can outperform traditional diagnoses.[229] Fourth, comprehensive assessment identifies patient's strengths (e.g., above-average cognitive functioning) and weaknesses beyond the focal problem, which can be used to tailor treatment.[226]

Implications for public health and prevention

Public health approach to psychotic disorders encompasses preventive interventions, early detection, and disorder burden assessment. The superspectrum model has implications for each.

Primary prevention is critical to ameliorating disability and suffering associated with psychotic disorders.[230] Prevention is particularly cost-effective when targeting high-risk groups.[231] Unfortunately, only a few risk factors for psychotic disorders are clearly established and their effects are modest.[94,232] Alternatively, selective prevention can be administered to people with nascent expressions of the superspectrum.[233] Diagnostic manuals offer little guidance for identifying these individuals, as traditional diagnoses (e.g., schizophrenia, bipolar disorder) describe full-fledged disorders, with the sole exception of attenuated psychosis syndrome (under Conditions for Further Study in DSM-5). In contrast, HiTOP provides a graded and multidimensional picture of subthreshold psychopathology. These vulnerabilities predict subsequent disorders[234,235] and can be detected as early as elementary school,[205] presenting an opportunity to intervene before clinical problems develop. A combination of subthreshold psychopathology, environmental, and genetic vulnerabilities may be needed to accurately identify at-risk individuals.

Existing preventive interventions cannot completely ameliorate the burden of psychotic disorders[230] and have to be complemented by early intervention programs. Traditional diagnostic assessments rely on extensively trained interviewers, whereas the superspectrum can be assessed by self-report measures, which are highly scalable, making them particularly suitable for early detection. This screening can be done in schools, primary care, or online to identify people who need care (with treatment eligibility confirmed by provider upon referral).

Public health statistics typically focus on numbers of cases. This underestimates true burden of the superspectrum, as it overlooks subthreshold symptoms in non-cases and differences in severity among cases. The dimensional approach allows calculation of the cumulative psychopathology burden across the full range of the superspectrum as well as calculation of traditional statistics (e.g., prevalence, incidence) using categories based on severity ranges.

Limitations and outstanding questions

Although substantial structural and validity evidence has accumulated in support of the superspectrum model, as reviewed here and in companion paper,[1] significant gaps remain. Table 3 highlights key gaps and poses testable hypotheses for each.

A first limitation is that mania and dissociation are included provisionally and need further research for definitive placement. Second, existing studies were largely limited to majority groups in Western societies, although there are some notable exceptions.[236,237] Evidence to-date indicates that the structure of psychopathology is remarkably robust across sociodemographic groups, although groups may differ substantially in their position on the superspectrum. Third, traditional course descriptors (e.g., number of episodes) do not naturally fit dimensions, rather dimensional constructs facilitate mapping of illness

trajectories and quantitative course characteristics. However, utility of these characteristics need investigation. Fourth, the HiTOP consortium is completing dedicated measures that will require rigorous validation. The existing validity evidence on the superspectrum model is very encouraging, but more studies are needed. Fifth, much of this research examined dimensions individually, but interactions among dimensions or with demographic factors may affect relations between dimensions and validators. These interactions need to be evaluated empirically. Sixth, the superspectrum does not include any biomarkers currently. However, if clear links between pathophysiologic processes and dimensions emerge as expected, this may enable construction of a unified nosology that integrates detailed clinical descriptions with informative biomarkers. Seventh, evidence of clinical utility is extensive for the superspectrum traits, but more data are needed on patients with frank psychosis. Dimensional assessment may be unnecessarily detailed for acute care, but full benefits of the superspectrum model are expected in outpatient and population health settings. Eighth, existing practice guidelines are tied to traditional disorders and will require translation to dimensional diagnosis. Ninth, clinical ranges are currently based on statistical deviance, and ranges tailored to a specific clinical action should be developed. It is especially important to determine the minimal elevation on a relevant dimension where a given therapeutic approach is indicated (i.e., offers positive cost-benefit trade-off).

Conclusions

The existing nosology and treatment strategies for psychosis-related psychopathology are largely heuristic. They rely on diagnostic entities that emerged from clinical lore and in important ways do not match what science has revealed about the nature of these conditions. This mismatch has limited reliability, validity, and clinical utility of traditional diagnoses. The superspectrum model follows a quantitative approach that offers greater precision in the characterization of presenting problems, treatment selection, monitoring of treatment response, and constructs for research. Further studies need to address several gaps, but existing knowledge is sufficient for implementation of the model in research and clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box.

Three examples of studies based on the superspectrum model

Example 1. Neuroimaging Study.

This hypothetical study is motivated by a prior neuroimaging finding of neural deficit X in people with schizophrenia. Within schizophrenia, the deficit correlates most strongly with negative symptoms. X has not been investigated in other disorders, but the superspectrum model predicts that it extends beyond schizophrenia. Accordingly, the study hypothesis is that in the general population X is related to detachment, and this link is stronger than the association between X and psychoticism.

Study participants are adults (age 18 – 60 years) recruited from the surrounding community. People with high scores on either detachment or psychoticism are oversampled, and people with low scores on either are undersampled (this is not a requirement of a dimensional design, but is done to maximize statistical power, as the sample size is constrained by the cost of neuroimaging). The only exclusion criteria are MRI rule-outs, inability to complete study assessments, and prior treatment with antipsychotics (a likely confound for this study). Sample size is determined by expected effect size and is no greater than would be required in a case-control design.

The Community Assessment of Psychic Experiences (CAPE),[251] a brief self-report measure, is used for sample selection. Enrolled participants complete measures of the 14 symptom components and traits within the superspectrum; the internalizing, somatoform, disinhibited externalizing, and antagonistic externalizing spectra; and cognitive and real-world functioning domains. This battery provides a comprehensive dimensional profile. Besides cognition, the constructs can be assessed entirely by self-report, but investigators opted for the iHiTOP interview for the most rigorous assessment.

Primary analyses will focus on associations of X with detachment and psychoticism, comparing them for a statistically significant difference. Secondary analyses will control for the other HiTOP spectra to further evaluate specificity of X to detachment. Also, X will be correlated with subdimensions of detachment, while controlling for the overall detachment score, and significant associations would indicate what elements of detachment are affected by X. Analyses will also test for non-linearity of the association between X and detachment using spline regression[252] to determine whether the association is continuous across levels of severity as assumed. Finally, moderated regression analyses will explore whether other dimensions (e.g., depression) moderate the association between X and detachment.

Example 2. Randomized Clinical Trial (RCT).

This study is motivated by the literature indicating that drug Y has efficacy in several psychotic disorders. This suggests that Y acts on a common pathophysiology underpinning the superspectrum. However, the evidence is less clear as to which symptoms respond to Y. Benefits have been observed for both psychoticism and detachment, but reduction in detachment may be secondary to improvement in psychoticism, a possibility that has not been rigorously tested. Accordingly, the primary

hypothesis of the study is that Y is efficacious for the superspectrum overall, but the study will also explore whether the drug has specific effects on its subdimensions.

Study participants are adults (age 18 – 60 years) recruited from an outpatient psychiatry clinic that serves a population with a variety of disorders. First, participants complete the Personality Inventory for DSM-5—Brief Form (PID-5-BF)[253] that assesses both psychoticism and detachment. The two scores are summed into a composite, and patients scoring in the top 2.5% of the general population norms are eligible for the study, as showing a clinically significant elevation on the superspectrum. The resulting sample is diagnostically heterogeneous, including participants with different psychotic disorders, personality disorders, or subthreshold but significant symptoms. Exclusion criteria are inability to complete study procedures and severe psychopathology (e.g., active suicidality, severe psychosis) that precludes participation in the placebo arm of the study. Eligible participants are randomized into 12 weeks of drug Y or placebo.

The primary outcome is the overall superspectrum severity. Multiple existing interviews can measure this outcome (Supplementary Table 1), but the investigators chose the iHiTOP as it provides comprehensive coverage. The superspectrum module of the iHiTOP is administered every two weeks starting at baseline to track changes in the total superspectrum score as well as reality distortion, disorganization, inexpressivity, and avolition subscales. The other HiTOP spectra, cognitive functioning, and real-world functioning are assessed at baseline and end of treatment to explore any unexpected treatment benefits. Traditional diagnoses are also assessed at baseline.

Primary analyses will compare the slope of the superspectrum score over time between Y and placebo. Analyses will also test whether diagnosis (e.g., schizophrenia spectrum vs. mood disorders with psychosis vs. personality disorder) moderates the difference between Y and placebo. Secondary analyses will be performed on residualized reality distortion, disorganization, inexpressivity, and avolition scores, with the variance common to these four scales factored out to isolate variance specific to each subdimension.[254] Trajectory analyses will test whether Y improves any of these subdimensions beyond its effect on the superspectrum. Effects of Y on other outcomes will be explored, controlling for the false discovery rate.

Example 3. Genome-wide association study (GWAS).

This study is motivated by evidence that detachment and psychoticism are only modestly correlated. However, existing GWAS have focused on diagnoses and thus were unable to differentiated genetic liabilities to these spectra. Study hypothesis is that the genetic correlation between psychoticism and detachment will be low to moderate, mirroring the phenotypic correlation.

Study participants are 50,000 adults (age 18 – 60) with the sample enriched for the target spectra by recruiting participants from supported housing services and community programs for people with mental illness as well as from outpatient psychiatry clinics. This sample size is sufficient for GWAS, as in population studies dimensional phenotypes offer greater statistical power than dichotomous phenotypes.[255] The study utilizes

recruitment centers in all 6 inhabited continents to maximize ancestral diversity. DNA is collected from saliva samples for feasibility across recruitment sites.

The primary measures are detachment and psychoticism traits on the HiTOP-SR. This measure was selected because traits are more stable over time, which tends to increase associations with genetic markers, and can be validly assessed by self-report, providing a highly scalable assessment. Self-report can be confirmed in a subsamples with the highest HiTOP-SR scores using trait version of the iHiTOP interview.

Primary analyses are GWAS of the spectra scores, analyzed within homogenous ancestry groups and meta-analyzed across ancestry groups. Parameters of primary interest are the genetic correlation between psychoticism and detachment, number of genome-wide significant loci for each, SNP-based heritability estimates of the spectra, and genetic correlations with previously-studied phenotypes (e.g., schizophrenia, bipolar disorder, autism, and cognitive ability).

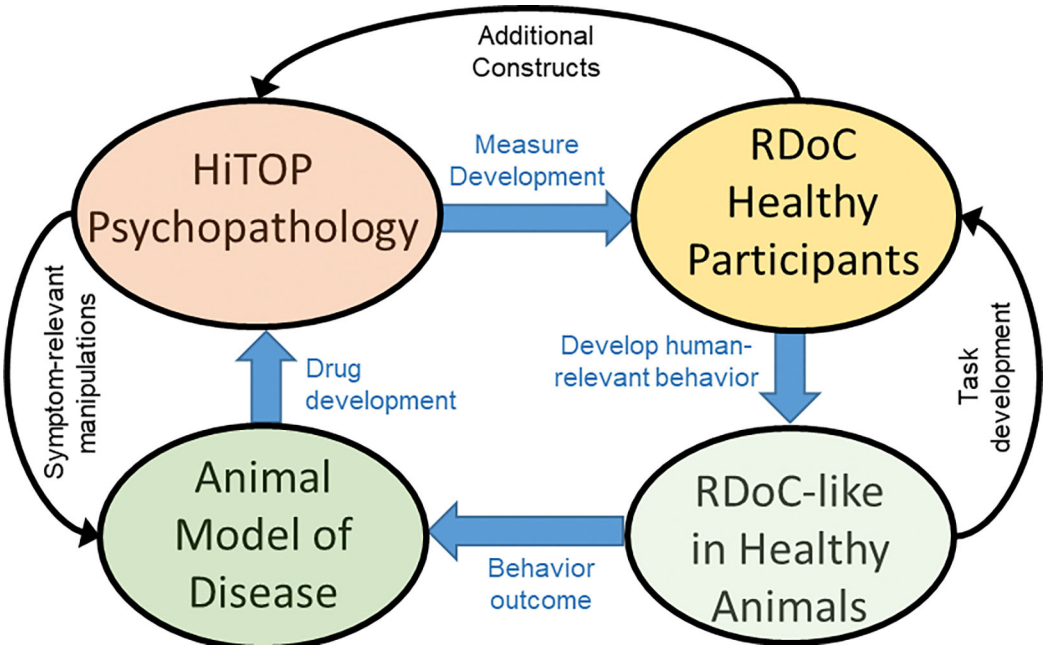

Figure 1. Utility of HiTOP for development of animal models

HiTOP has been designed explicitly to describe psychopathology in patient populations, whereas RDoC is a model of basic biobehavioral functions. HiTOP can benefit by including constructs identified by RDoC that in their extreme manifestations constitute psychopathology. Conversely, validation vis-a-vis HiTOP constructs can guide development of measures for RDoC to ensure their relevance for psychopathology. Behavioral assessments included in RDoC can be translated into animal behavioral testing (RDoC-like). Conversely, some animal tests can be reverse-translated to humans for RDoC constructs (task development). Once these cross-species behavioral paradigms are established, they can be used to assess animal models of psychopathology (behavior outcome). Animal models also require genes and environmental factors related to psychopathology (symptom-relevant manipulation), which HiTOP helps to identify. The resulting animal diseases models can be used for drug development to treat psychopathology. HiTOP and RDoC can be applied jointly to develop more psychopathology-relevant animal models than has been possible with traditional diagnoses.

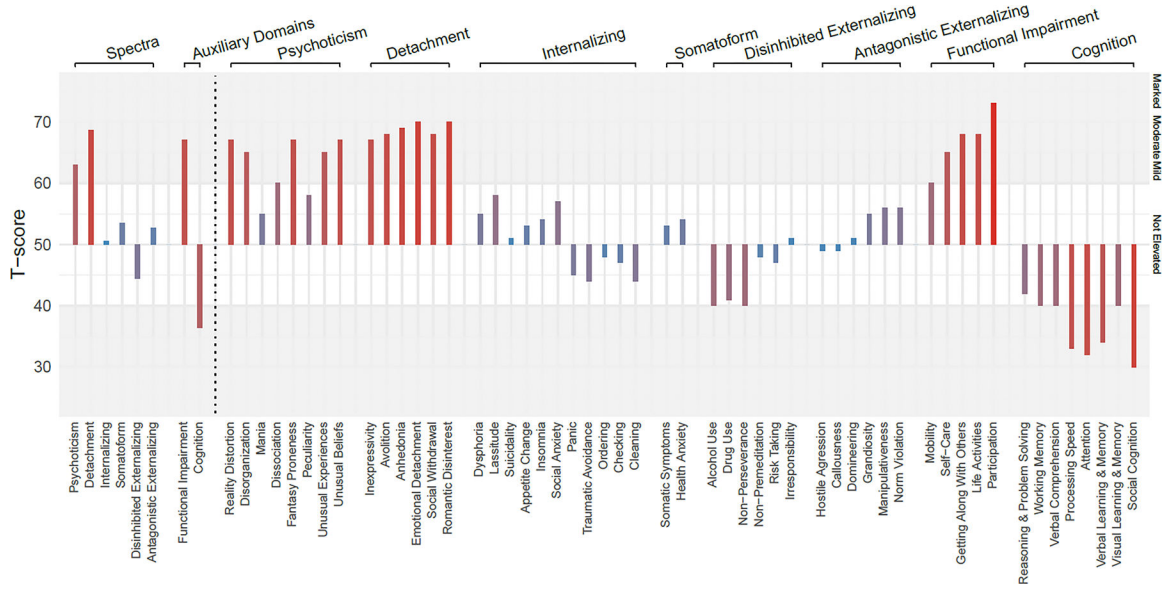

Figure 2. Illustrative profile diagnosis of a patient with psychosis

Note: Assessment results are expressed as 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).

Table 1.

Behavioral assessments of the superspectrum constructs for cross-species translational research

	Domains	Trait/Symptom	Animal Test	Human Test Analog	Reference
Psychosis Superspectrum	**Psychoticism (Thought Disorder) spectrum**	Fantasy Proneness	N/A		
		Unusual Beliefs	N/A		
		Unusual Experiences	N/A		
		Peculiarity	N/A		
		Reality Distortion	N/A		
		Disorganization	N/A		
		Dissociation	N/A		
		Mania	Mouse and rat BPM	Human BPM	238
	Detachment spectrum	Emotional Detachment	N/A		
		Anhedonia	EBDM and PRBT	EBDM and PRBT	239,240
		Social Withdrawal	Social Withdrawal		241
		Romantic Disinterest	Sexual interest		242
		Inexpressivity	N/A		
		Avolition	EBDM and PRBT	EBDM and PRBT	239,240
Auxiliary Domains	**Cognition**	Attention/vigilance	5-Choice serial reaction task	Continuous Performance Test, Identical Pairs	243
		Working Memory	Radial Arm Maze	Spatial Working memory	244
		Processing Speed	Choice reaction-time tasks	Choice reaction-time tasks	245
		Visual Learning & Memory	TUNL and Delayed matching	Delayed matching	246
		Verbal Learning & Memory	N/A		
		Social cognition	N/A		
		Reasoning & Problem Solving	Attentional Set-Shifting Task	Mazes test	247
		Verbal Comprehension	N/A		
	Functional Impairment	Mobility	Rotarod/Gait analysis	Gait analysis	248
		Self-Care	Grooming/Nest building etc.		249
		Getting Along	Social Interaction	Social Interactions	250
		Life Activities	N/A		
		Participation	N/A		

Note: Human test analog is listed only when an animal test is available. Avolition and anhedonia are represented by the same tasks, because existing tasks do not clearly distinguish between these constructs. N/A = not applicable; BPM = Behavioral Pattern Monitor; EBDM = effort-based decision making; PRBT = progressive ratio breakpoint task; TUNL = Trial-Unique, Nonmatching-To-Location task.

Table 2.

Explanatory and predictive power of quantitative nosology compared to traditional diagnoses in patients with psychotic disorders

Reference	Sample size	Validator	Value of R^2		Ratio Quantitative/Traditional
			Quantitative	Traditional	
Concurrent					
[177]	933	Biotype[a]	0.388	0.099	3.94
[176]	150	Cognitive functioning	0.310	0.028	11.07
[178]	980	Overall functioning	0.237	0.078	3.04
[176]	150	Observed functioning	0.221	0.056	3.95
[176]	579	Self-reported social functioning	0.182	0.048	3.79
[178]	980	Personal care	0.177	0.064	2.77
[176]	150	Informant-rated functioning	0.095	0.033	2.88
[178]	980	Mental health crises	0.095	0.055	1.73
[176]	579	Cognitive functioning	0.089	0.083	1.07
[178]	980	Service utilization	0.085	0.069	1.23
Mean concurrent					**3.50**
Predictive					
[179]	316	Remission	0.340	0.250	1.36
[179]	316	Recovery	0.270	0.140	1.93
[179]	316	Public assistance	0.240	0.130	1.85
[179]	316	Social functioning	0.230	0.060	3.83
[179]	316	Role functioning	0.220	0.110	2.00
[179]	316	Unemployment	0.180	0.090	2.00
[179]	316	Cognitive functioning	0.150	0.170	0.88
[179]	316	Self-reported functioning	0.150	0.070	2.14
[179]	316	Residential independence	0.110	0.100	1.10
[179]	316	Diabetes onset	0.100	0.050	2.00
[179]	316	Educational attainment	0.100	0.060	1.67
[179]	316	EEG (P300)	0.070	0.010	7.00
[179]	316	EEG (mismatch negativity)	0.060	0.030	2.00
Mean predictive					**2.29**

Note: Review of studies published since 2000 in patients with psychotic disorders. Pseudo-R^2 is reported for analyses that examined dichotomous validators. Both quantitative and traditional nosologies were assessed by interview. Overlapping validators were not included to avoid biasing in the comparison (e.g., when a composite cognitive index was included, individual cognitive tests were not). Concurrent validators reflect status currently or up to 12 months before the interview. Predictive validators are outcomes 20 years after the interview.

[a]The study reported area under the curve statistic, and we converted it to R^2.

Table 3.

Falsifiable hypotheses for future research

Research direction	Hypothesis
Provisional constructs	Further research on the latent structure of psychopathology will confirm placement of mania and dissociation on the superspectrum.
Understudied societies and sociodemographic groups	Structural studies outside majority groups and Western societies will replicate the psychosis superspectrum, psychoticism and detachment spectra, and their 14 lower-order dimensions.
Trajectories	Longitudinal research will explicate trajectory features (e.g., mean level, variability, slope of time) that characterize the superspectrum over time. Moreover, these features will be more informative of etiology and long-term outcome of patients than traditional course features (e.g., age of onset, number of episodes, illness duration etc).
Measurement	HiTOP-based measures (self-report, informant-report, and interview) currently in development will show reliability and validity that is equivalent or superior to existing instruments (Supplementary Table 1), while offering a comprehensive assessment.
Validity	Further studies that directly compare validity of the superspectrum model to DSM-5 diagnoses will confirm the 2-fold increase in explanatory and prognostic power for etiology, pathophysiology, service needs, and long-term outcomes.
Interactions	Validity studies will test interactions of the superspectrum dimensions with other HiTOP constructs and demographics (e.g., detachment with depression, reality distortion with age, etc) when explaining etiology, treatment response, and outcome. We hypothesize that a number of interactions proposed by existing theories will be confirmed. This will further increase explanatory and prognostic power of the superspectrum model.
Biomarkers	Stronger links between pathophysiology and dimensions, compared to disorders, will enable research to identify useful biomarkers of the superspectrum.
Clinical Utility	Surveys of physicians who received training in the superspectrum model will confirm that it is more useful than psychotic disorder diagnoses in outpatient settings. Another hypothesis is that implementation of the superspectrum assessment will improve treatment outcomes compared to assessment as usual.
Practice guidelines	Given that traditional diagnoses and dimensional profiles are based on the same symptoms, although organized differently, it will be possible to translate many disorder-based practice guidelines to elevations on dimensions. Another hypothesis is that translated guidelines will be confirmed in randomized clinical trials based explicitly on the superspectrum model.
Clinical ranges	Further research will explicate clinical ranges that indicate the need for a particular clinical action (e.g., initiate treatment with a dopamine receptor blocker, admit to partial hospitalization program, etc).