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Psychosis Superspectrum I: Nosology, Etiology, and Lifespan Development

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Abstract

This review describes the Hierarchical Taxonomy of Psychopathology (HiTOP) model of psychosis-related psychopathology, the psychosis superspectrum. The HiTOP psychosis superspectrum was developed to address shortcomings of traditional diagnoses for psychotic disorders and related conditions including low reliability, arbitrary boundaries between psychopathology and normality, high symptom co-occurrence, and heterogeneity within diagnostic categories. The psychosis superspectrum is a transdiagnostic dimensional model comprising two spectra—psychoticism and detachment—which are in turn broken down into fourteen narrow components, and two auxiliary domains—cognition and functional impairment. The structure of the spectra and their components are shown to parallel the genetic structure of psychosis and related traits. Psychoticism and detachment have distinct patterns of association with urbanicity, migrant and ethnic minority status, childhood adversity, and cannabis use. The superspectrum also provides a useful model for describing the emergence and course of psychosis, as components of the superspectrum are relatively stable over time. Changes in psychoticism predict the onset of

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psychosis-related psychopathology, whereas changes in detachment and cognition define later course. Implications of the superspectrum for genetic, socio-environmental, and longitudinal research are discussed. A companion review focuses on neurobiology, treatment response, and clinical utility of the superspectrum, and future research directions.

Limitations of traditional diagnosis

Traditional diagnoses of psychotic disorders, codified in the 5th edition of Diagnostic and Statistical Manual (DSM-5)[1] and 11th edition of International Classification of Diseases (ICD-11),[2] face major limitations. First, reliability of diagnoses is low. Interrater kappa ranged from .40 to .56 for schizophrenia, schizoaffective disorder, and bipolar disorders in the DSM-5 Field Trials.[3] Likewise, the temporal stability of these diagnoses is low, with kappa of .13 to .65.[4] Reliability problems are inherent in the categorical diagnosis, because extensive evidence indicates that symptoms of psychotic disorders are distributed continuously in the general population, making any diagnostic boundary arbitrary.[5–7] In particular, the modal case is just above the threshold, and even more people fall right below the threshold, so small shifts in symptom report change diagnosis for many people.[8] Moreover, numerous people experiencing subthreshold symptoms are not captured by traditional diagnoses despite substantial symptom burden.

Second, symptoms of psychotic disorders often co-occur with mood, substance use, and personality pathology symptoms.[9–11] Traditional systems deal with this problem by creating mutually-exclusive diagnoses. This leads to proliferation of diagnostic categories and obscures commonalities among them in etiology and treatment response.[12] Moreover, reasons for the high co-occurrence are ignored. These cross-cutting relationships can be described by transdiagnostic models of psychopathology. Meta-analytic evidence indicates the co-occurrence symptoms of psychotic disorders reflects two underlying dimensions —psychoticism and detachment—that are interrelated and jointly form the psychosis superspectrum.[11]

Third, psychotic disorders are heterogeneous. For example, positive and negative symptoms are uncorrelated among individuals with psychotic disorders,[8,13,14] implying these symptoms reflect different processes. Traditional subtypes proved ineffective in characterizing this heterogeneity,[15] but dimensional models revealed a consistent set of homogeneous constructs within the psychosis superspectrum.[16–20]

These problems are unsurprising, given that the mutually-exclusive nature of psychotic disorders was assumed, rather than inferred from data,[6] an assumption that accumulated evidence contradicts.[21] In addition, the traditional strategy for developing diagnoses focuses on external validity, and the process for proposing diagnostic criteria is not specified.[22,23] Consequently, a diagnosis may have external validity but lack internal coherence. For example, Emil Kraepelin sorted patients into groups to maximize schizophrenia's (dementia praecox's) prognostic value.[24] The resulting criteria are useful for prediction, but capture a group heterogeneous in clinical presentation and etiology, which undermines the value of diagnosis for treatment selection and drug development.[25–27]

An alternative strategy for nosologic discovery is construct validation, which systematically considers both external and internal validity.[28] Factor analysis and structural equation modeling were developed to implement this approach.[29,30] It begins by examining empirical associations among elements of psychopathology (e.g., signs and symptoms) to identify coherent and distinct constructs, which are then related to external criteria to determine their utility. This approach helped to develop classifications of affect, personality, and cognitive abilities.[31–33] In psychiatry, it produced influential models and measures, such as the Child Behavior Checklist and Positive and Negative Syndrome Scale.[34–37]

This review describes the application of a construct validation approach to the nosology of psychotic disorders. The emerging quantitative nosology has generated a substantial literature reviewed in a prior publication.[12] This review provides major updates based on new literature, expands on prior publications by addressing cognitive and functional impairment in psychosis, and covers new topics such as lifespan development.

The psychosis superspectrum in the Hierarchical Taxonomy of Psychopathology (HiTOP)

Principles.

The main objective of the HiTOP consortium—a collaboration of 175 psychologists and psychiatrists—is to improve the utility of psychiatric nosology for clinicians and scientists. HiTOP resolves the problem of arbitrary categories by using tools such as factor analysis and structural equation modeling to identify constructs which most parsimoniously describe observed correlations among symptoms.[38] This approach produces reliable descriptions of psychopathology. For example, it decomposes the heterogeneous schizophrenia category into multiple symptom components that are highly internally consistent (Cronbach's α ranging from 0.76 to 0.90).[14,39,19] Constructs in the HiTOP model are based on symptom-level data, so the model itself is descriptive and does not speak to the factors driving that structure. However, greater reliability of measurement facilitates research into psychopathology's causes and consequences.

The HiTOP approach addresses the problem of comorbidity through a hierarchy of constructs, from narrow to broad (depicted in Figure 1). As an example, symptom components that are highly related (e.g., inexpressivity and avolition) are grouped into the higher-order detachment spectrum. Detachment is related to the psychoticism spectrum, and together they form the psychosis superspectrum. At the broadest level, comorbidity between the psychosis superspectrum and other psychopathology is reflected by a general factor, or p-factor. This hierarchical approach results in coherent constructs at multiple levels of specificity, capturing comorbidity through higher-order dimensions above the level of traditional diagnoses, as well as symptom heterogeneity within diagnoses through more specific constructs. For example, two individuals with severe detachment may be differentiated by their unique profiles of narrower components, such as romantic disinterest and anhedonia. Unlike the DSM hierarchy of chapters and diagnostic specifiers, HiTOP superspectra and components were identified through converging results from structural analyses of large, epidemiological and clinical datasets.

HiTOP addresses arbitrary thresholds of severity through dimensional constructs. All HiTOP components are operationalized as continua, ranging from mild (e.g. social apprehension, unusual ideas) to severe (e.g. complete lack of social relationships, bizarre delusions). This facilitates the study and description of psychopathology along the same dimensions from the first signs observed in childhood, to first episode, to remission.

Model Content.

Figure 1 depicts the resulting model, a hierarchy of dimensional constructs. A meta-analysis of 35 structural studies comprising data from over 120,000 individuals describes the psychosis superspectrum defined by psychoticism and detachment, which together encompass psychotic disorders and some personality disorders, including schizotypal, schizoid, paranoid, and avoidant personality disorders.[11]

The HiTOP constructs outlined in Figure 1 are defined in Table 1. The superspectrum includes both maladaptive traits and symptom components. Usually components and traits parallel each other, and they are distinguished by timeframe: components capture psychological states (e.g., current or past month) and traits capture stable predispositions to these states.[40] Indeed, evidence indicates clear alignment and continuity between positive schizotypy traits and positive symptoms as well as negative schizotypy traits and negative symptoms.[12,41] However, some components (e.g., mania) and traits (e.g., fantasy proneness) do not have complements at the state or trait level. The superspectrum does not include depression because it falls within the emotional dysfunction superspectrum, and substance abuse because it is within the externalizing superspectrum.[11,42,43] Instead, co-occurrence of psychosis with depression and substance misuse is captured by the general factor (p-factor), which reflects the tendency towards co-occurrence shared by most forms of psychopathology.[44]

Within the detachment spectrum, symptom components include inexpressivity and avolition, typically termed negative symptoms.[12] Detachment also encompasses more stable traits and less severe forms of psychopathology via the maladaptive traits of emotional detachment, anhedonia, social withdrawal, and romantic disinterest (see Supplemental Table 1 in the companion paper for measures of detachment).[45] At their most severe, these traits can also be considered negative symptoms, but commonly exist at lower levels of severity. Within the psychoticism spectrum, symptom components include reality distortion (hallucinations and delusions), disorganization, and provisionally, dissociation and mania. Mania's placement is provisional because it shifts between psychoticism and internalizing spectra depending on the sample prevalence of mania and the assessment method.[44,46–48] Dissociation's placement is provisional because few structural studies included dissociation, although there is strong indirect evidence for its placement on the psychoticism spectrum.[12,49] Dissociation encompasses anomalous self-experiences and other symptoms associated with disorders of self, which merge with dissociation in structural analyses.[16] The spectrum also includes the maladaptive traits of fantasy proneness, unusual experiences, unusual beliefs, and peculiarity.[12]

Some structural studies propose more detailed models of symptoms and traits within these spectra.[50–52] The HiTOP consortium is developing both a self-report measure and

structured interview assessing detachment and thought disorder,[16,53] which include many more maladaptive traits and symptom components. This work is ongoing, so the current model includes only the best-established lower-order constructs. The measure development process may validate more specific constructs, or may reveal that further differentiation is useful. Notably, the superspectrum is similar to the "psychosis spectrum" described by Guloksuz and van Os,[54] with two small differences. First, Goluksuz and van Os's spectrum includes depression, whereas depression is assigned to the internalizing spectrum in HiTOP. Second, the HiTOP psychosis superspectrum emphasizes the bifurcation of psychoticism and detachment, whereas Guloksuz and van Os focus on the broadest common factor of the psychosis superspectrum, rather than its elements.

Auxiliary domains.

While cognitive and functional deficits are central to the psychosis superspectrum, they have not yet been incorporated into the core HiTOP model. Accordingly, they are discussed here as auxiliary domains, with the intent that future revisions will formally include them.

The cognitive deficits associated with psychosis are broad, therefore the cognitive domain includes the same cognitive abilities in which the general population varies: processing speed, attention, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, verbal comprehension, and social cognition.[55] The HiTOP model of cognition vis-a-vis the psychosis superspectrum mirrors the domains identified by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Neurocognition Committee.[56] Note that while the MATRICS Committee concluded that verbal comprehension was impaired in schizophrenia, verbal comprehension was not included in the MATRICS battery, because the battery was designed to facilitate treatment development, and verbal comprehension is a very stable cognitive ability.[56] However, since verbal comprehension is relevant to the description of psychosis,[57] it is included here. Cognitive deficits associated with the psychosis superspectrum are largely trait-like.[58,59]

Cognitive deficits are a core feature of schizophrenia and related to most forms of psychopathology in the superspectrum. Cognitive decline precedes schizophrenia onset and is an important determinant of outcomes among people with schizophrenia.[60] Cognitive abilities in other non-affective psychoses, bipolar disorder, and schizotypal personality disorder are intermediate between abilities observed in schizophrenia and healthy controls.[61–64] Generalized cognitive impairment is particularly closely linked to the detachment spectrum, notably negative symptoms, and disorganization, but not reality distortion symptoms.[65–67]

Cognitive deficits are not limited to the superspectrum—they are observed in many other mental disorders,[68] particularly disinhibited externalizing psychopathology[69]—but deficits are generally the largest in schizophrenia and bipolar disorder.[68,70] How strongly cognition relates to underlying spectra is unknown. Cognitive deficits are listed as an auxiliary spectrum due to a lack of studies that examined the structure of psychopathology and cognitive functioning together. Further research is needed to determine which cognitive impairments are specific to the superspectrum, and which symptoms and traits within

the psychosis superspectrum are most closely linked to various cognitive impairments. The HiTOP model can facilitate this research providing a comprehensive assessment of psychopathology across all severity levels, appropriate to both clinical and population samples. Box 1 illustrates an application of HiTOP to such a study design.

Psychotic disorders are associated with functional decline. In the DSM, functional impairment or decline is incorporated into the diagnostic criteria. In the HiTOP model, functioning is assessed as a separate domain,[71] and hence is included here as an auxiliary spectrum. This disentangles psychological dysfunction (e.g., paranoid ideation) from its sequelae for relationships, occupation, recreation, etc. The approach also facilitates tracking improvement and deterioration in functioning as well as in symptoms, as functional impairment may persist even in symptom remission.[72] HiTOP captures classically deteriorating cases through elevations on both symptoms and functional impairment, but also describes people who diverge from this common pattern. This approach is consistent with the distinction that ICD-11 makes between disorder and disability.[73]

Functional impairment is multidimensional.[74] The HiTOP model of functional impairment is based on the World Health Organization's Disability Assessment Schedule (WHO-DAS),[75] as the WHO-DAS was developed following the same principals of construct validation used to construct the HiTOP model.[76] Functional impairment comprises mobility, self-care, getting along with others, life activities, and participation. The HiTOP model of functional impairment does not include a "cognition" domain, as this is well-described through the cognitive domain, and because self-reported cognitive ability is weakly correlated with psychometrically measured cognitive ability.[77]

The remainder of this review describes the genetic architecture, socio-environmental risk factors, and developmental trajectories of the superspectrum from the prodromal stage to late adulthood. The companion review covers neurobiology, animal research, and utility of the superspectrum model for treatment.[45] Notably, diagnostic language is used to describe findings based on diagnostic phenotypes, which account for a majority of the extant literature. However, HiTOP allows us to move beyond the case-control design to multidimensional phenotypes, which describe continua of severity at various levels of specificity. Therefore, findings from diagnostic research are summarized in diagnostic terms, followed by statements describing their relevance to the psychosis superspectrum. Throughout both papers, implications for future research are discussed.

Genetic architecture of the superspectrum

The structure of genetic risk for psychosis and related psychopathology largely mirrors the phenotypic structure of the psychosis superspectrum. The estimated heritability of the psychosis superspectrum based on behavioral genetic research is 73%.[78] Molecular genetic research also indicates common genetic risks underly psychotic disorders. The high genetic correlation between schizophrenia and bipolar disorder (r_g=0.68)[79] outlines a psychoticism dimension in genomic structural equation models.[80] Within the superspectrum, behavioral genetic methods identify a genetic factor underpinning psychoticism,[81–83] and a distinct factor underlying detachment.[83–85] Schizophrenia GWAS appear to capture genetic variance underlying both psychoticism and detachment, as the schizophrenia polygenic risk score,

which quantifies common genetic risk associated with the schizophrenia diagnosis, has sometimes been associated with measures of psychoticism,[86] and sometimes with measures of detachment.[87] In aggregate, however, polygenic risk for schizophrenia has more often been associated with detachment in both people with psychotic disorders[88,89] and in population samples.[90,91]

Both behavioral and molecular genetic research identify strong genetic links between detachment and cognition. Behavioral genetic methods indicate that a large majority of the covariance between schizophrenia and cognition is driven by shared genetic risk factors.[92–95] In molecular genetic approaches, shared genetic risk factors underlying the psychosis superspectrum and cognition are indicated by the significant genetic correlations between schizophrenia and intelligence. Genetic risk for schizophrenia has been shown to predict cognitive deficits in cases,[87] nonpsychotic adults,[96] and adolescents.[89,97] The lack of a genetic correlation between bipolar disorder and intelligence (r_g=−0.09)[79] likely reflects that the association between detachment and cognition is stronger than that linking psychoticism and cognition, discussed above.

The genetic structure of symptom components is tentatively parallel to the phenotypic structure of the superspectrum. Behavioral genetic approaches in population samples estimate the heritability of symptom components ranges from 31–60%.[98] A molecular genetic analysis of the Northern Finland Birth Cohort, a sample of non-psychotic individuals, identified a close genetic correlation between physical and social anhedonia (elements of detachment), moderate genetic correlations between hypomania and unusual experiences (elements of psychoticism), and weaker or even negative correlations between these two symptom clusters, mirroring the organization of the detachment and psychoticism spectra.[99] While molecular genetic research has not yet identified replicable SNPs associated with specific symptoms of the psychosis superspectrum, a mega-analytic GWAS of three population-based samples of adolescents identified distinct, significant genetic liabilities for anhedonia, negative symptoms, and cognitive disorganization,[100] the latter two symptom dimensions of which had significant genetic correlations with the schizophrenia diagnosis. Although evidence for specific genetic liabilities at narrower levels of the hierarchical model is weak, largely due to the difficulty of obtaining thorough phenotypic data on samples large enough for genetic analyses, the aforementioned analyses indicate the potential to parse genetic components of the psychosis superspectrum.

The analyses described above indicate common genetic risks underpin both subthreshold symptoms and traits and more severe symptoms. Behavioral genetic research identifies a dose-dependent association between familial history of psychotic disorders and psychotic symptoms across the continuum of severity, from no symptoms to subclinical forms of psychoticism, to psychotic disorders.[101,102] Family transmission study showing siblings of probands with schizophrenia are more likely to have schizotypal personality disorder and other non-affective psychoses.[103–105] Schizoid personality disorder is also more common among relatives of probands with schizophrenia and other non-affective psychoses[106,107] compared to relatives of individuals with affective psychosis and controls. Genetic risk is specific to disorders within the psychosis superspectrum, as rates for affective and anxiety disorders among siblings were not elevated.

There is some evidence that psychotic experiences in the general population may be genetically more closely correlated to major depression (r_g=0.46) and autism (r_g=0.39) than schizophrenia (r_g=0.21).[108] However, comparisons of GWAS of subthreshold symptoms and case-control GWAS are confounded by differences in the mode of assessment (self-reported versus interviewer-rated symptoms), and by the exclusion of cases from these analyses, which truncates the dimension at its upper ranges. Its notable that parent-reported subthreshold symptoms reported in Pain and colleagues[100] have significant genetic correlations with schizophrenia, and polygenic risk for self-reported psychotic experiences in the general population predict development of psychosis,[108] supporting a link between subthreshold reality distortion and more severe degrees of psychoticism.

A HiTOP-based approach to gene discovery may help disentangle genetic liability for psychoticism, detachment, and cognition. Genetic risk for psychotic disorders is largely attributable to the cumulative effect of many common variants, and therefore approximates a normal distribution.[109] Dimensional phenotypes, such as those described by the HiTOP psychosis superspectrum, most closely match the underlying distribution of genetic risk, and thereby increase statistical power for gene discovery.[110] While the polygenic risk score for schizophrenia has often been associated with measures of detachment, indicating schizophrenia GWAS capture some degree of genetic variance underlying detachment, there has not yet been a GWAS with detachment itself as the target phenotype. A GWAS of psychoticism, detachment, and cognitive deficits has the potential to attenuate the high correlations among bipolar disorder, schizophrenia, and intelligence, and improve the specificity of genetic prediction. The hierarchical aspect of the model also has advantages for gene discovery. Directly phenotyping higher-order spectra has the potential to increase power for gene discovery, as suggested by novel genomic and transcriptomic hits identified via the psychoticism factor in genomic and transcriptomic structural equation models.[80,111] As a complement, assessing narrower traits and states may increase the specificity of genetic findings and improve genetic prediction.[112]

In sum, both behavioral and molecular genetic methods indicate a common genetic liability underlies psychotic disorders, consistent with the HiTOP psychosis super-spectrum. More specific genetic risks underlying psychoticism and detachment have been identified in behavioral genetic research, but structural analyses of molecular data are limited by the lack of large-scale GWAS of the detachment spectrum. The fine-grained genetic structure of the super-spectrum remains unclear. Genetic research implementing assessments of the psychosis super-spectrum, or using the super-spectrum as a model for investigating genetic structure, can distinguish many of the factors confounded by case-control genome-wide association studies.

The superspectrum and socio-environmental risk factors

A wealth of evidence implicates socio-environmental factors in the etiology of the psychosis superspectrum. These factors include urbanicity,[113–115] migrant and ethnic minority status,[116–119] childhood adversity,[120–123] and cannabis use.[124–127] Meta-analyses on contributions of these socio-environmental factors suggest that each increases risk

of psychotic disorder 2- to 4-fold,[113,117,123,125,127] the effects show a dose-response gradient,[124,125,127–129] and population attributable risk fractions are 20%–35%.[125,130,131]

Minority status increases risk of symptoms across the psychosis superspectrum, although evidence for the link between minority status and psychoticism are stronger than links with other spectra. Elevated incidence of non-affective and affective psychotic disorders has consistently been found in migrant and ethnic minority groups across several countries.[116–119] The largest incidence study to date confirmed this effect in 6 European countries.[116] Few studies have investigated associations between ethnic minority status and specific symptom components of the psychosis superspectrum, but those that have find more severe reality distortion in patients from ethnic minority than from majority groups.[132–134] Ethnic minority status also has been linked to greater reality distortion in the general population.[7,135,136] These effects can be explained, at least in part, by greater exposure to social adversity among minorities.[118,119,137] Ethnic minority status is also associated with greater detachment[132,133,138] and disorganization,[133,134] albeit these effects are weaker and less consistent.

Associations between urbanicity and individual symptom components of the psychosis superspectrum are understudied. Available evidence suggests that urbanicity is associated with more severe detachment and disorganization among cases.[134] In the general population, research generally focused on effects of urbanicity on reality distortion.[115,139,140] Given the temporal priority and dose-response gradient in effect of urbanicity on the superspectrum,[114] confounds such as social drift are unlikely to account for this effect. However, the association between urbanicity and psychotic disorders does not seem to hold in low- and middle-income countries, where urbanicity may index greater access to resources in some societies and greater exposure to adversity in others.[141] Hence, the role of contextual and area-level factors is central for understanding the role of urbanicity in the superspectrum.

Extensive evidence supports the role of childhood adversity as an important risk factor for the psychosis superspectrum.[120,121,123,142,143] The effect has been reported for both traits and symptom components. At trait level, consistent evidence indicates association with psychoticism, and emerging evidence supports an association with detachment.[144,145] At symptom level, a clear link has been consistently reported for reality distortion, whereas associations with detachment and disorganization are substantially weaker.[120,146] Childhood adversities are associated with various forms of psychopathology, but there is preliminary evidence that certain types of exposures are relatively specific to the psychosis superspectrum, including interpersonal violence, hostility, and threat.[128,143] This potential specificity needs to be verified further by taking careful account of exposure timing and validity of symptom outcome measures.

Cannabis use has been consistently linked to psychopathology across the psychosis superspectrum,[126,147–150] with the weight of evidence supporting a dose-dependent association between cannabis and psychoticism specifically.[127,151] Furthermore, psychotic disorders were strongly associated with premorbid exposure to high-potency cannabis in a recent large study in 6 European countries.[125] In the general population, numerous studies observed that cannabis use predicts future reality distortion symptoms.[7] Some studies

also found an increase in detachment, although the effect is much less consistent,[152] and no data are available on disorganization. In patients, cannabis exposure has been linked to elevated reality distortion, whereas no consistent effect was observed for detachment and disorganization.[153–155] Research on maladaptive traits found the strongest associations between cannabis use and unusual experiences and beliefs, whereas links to disorganization and detachment were weaker.[124,156]

Overall, some methodological issues remain in validating associations between socio-environmental exposures and the psychosis superspectrum. Especially notable is the relative emphasis in epidemiological research on identifying risks linked to psychoticism, rather than detachment. Other outstanding issues include possible reverse causality, confounding by genetic and other factors, and publication biases. Nevertheless, the available evidence indicates each factor contributes most strongly to reality distortion and related traits of unusual experiences and unusual beliefs. The effects on disorganization and detachment are weaker, and an important research priority is to identify socio-environmental factors specific to these elements of the superspectrum. The diathesis-stress model hypothesizes genetic vulnerabilities moderate effects of socio-environmental factors on psychopathology.[157,158] While there are some promising results in large studies,[159] most gene-environment interactions await replication.

Development of the Superspectrum

The psychosis superspectrum has its origins in childhood, long before the emergence of clinically significant symptoms. Below we review the trajectories of psychoticism, detachment, cognitive impairment, and functional impairment from childhood, through the clinical-high risk for psychosis (CHR-P) phase, into first episode and post-onset periods.

Development of psychoticism.

Individual differences in psychoticism are apparent by middle school.[160] These traits show moderate rank-order stability from age 7 to age 12,[161] from early adolescence to late adolescence,[162–164] and from late adolescence to early adulthood (r=0.33–0.42).[165] Early-life psychoticism predicts subsequent onset of psychotic disorders,[166–168] and is a risk factor primarily for reality distortion symptoms.[169–171]

CHR-P can be considered an intermediate stage between subclinical manifestations of psychoticism observed in childhood and reality distortion typically emerging in early adulthood. The vast majority (85–95%) of CHR-P individuals meet criteria based on the presence of attenuated psychotic symptoms—that is, subthreshold reality distortion—and the rest either have brief, limited psychotic symptoms or genetic risk and functional deterioration.[172,173] Although CHR-P status emphasizes the *state* of experiencing subthreshold psychoticism, risk *traits* are also apparent in this population. Paranoid and schizotypal personality disorders are common among CHR-P cases.[174] Nevertheless, psychoticism abates among a sizable fraction of the CHR-P population,[175] implying significant state variability.

CHR-P is a prodromal stage specific to the psychosis superspectrum. Although over half of CHR-P cases meet criteria for non-psychotic disorders,[172,173] these rates of comorbidity are comparable to rates observed in schizophrenia,[176,177] and CHR-P cases are not at an increased risk for onset or persistence of non-psychotic disorders.[178,179] Additionally, most CHR-P individuals do not progress to threshold psychosis,[180] consistent with the conceptualization of reality distortion as a continuum in which subthreshold experiences are more common than persistent psychosis.[181]

Over 2–3 years, reality distortion progresses to full psychotic intensity among 15–25% of CHR-P individuals.[182] Reality distortion symptoms are the strongest predictor of transition to psychotic disorder in CHR-P,[166,183] but personality disorders do not consistently predict transition.[174] This may be due to their heterogeneity, as conditions such as schizotypal personality disorder encompass both psychoticism and detachment. Importantly, transition is defined as reality distortion reaching the intensity of frank and persistent hallucinations or delusions; hence, psychoticism is more relevant to predicting transition than detachment (i.e., for a person whose reality distortion is just short of frank psychosis, even a small exacerbation would result in transition).[184] Were there a parallel concept of transition to pathological detachment, presumably milder manifestations of detachment would predict transition better than reality distortion.

Psychoticism is relatively stable in the post-onset period. Studies of people with personality disorders found a 10-year stability coefficient of r=0.66 for psychoticism.[185] In cohort of individuals with psychotic disorders, psychoticism symptoms are somewhat less stable.[14,186] For example, a 20-year follow-up of patients with first-admission psychosis found stability of psychoticism to be r=0.21.[14]

Mean-level symptom trajectories provide another perspective on course. However, trajectories can be affected by the choice of baseline, as studies beginning at first admission with psychosis observe an initial decrease in symptoms due to treatment initiation and regression to the mean (i.e., all participants are in a psychotic episode at baseline due to the sampling strategy, but many will be in remission at each follow-up). When the baseline is not tied to a common event (e.g., baseline is several months after first admission), trajectories of psychoticism are largely flat for the next 10 to 20 years.[187–189] This indicates the average symptom burden remains consistent, although individual patients may improve or worsen over time. Likewise, schizotypal personality disorder follows a steady long-term symptom trajectory.[190]

In sum, psychoticism as a trait emerges in childhood. Those with elevated psychoticism in early adolescence are most likely to experience clinically-significant psychoticism in the future. However, psychoticism is more variable than other spectra in the HiTOP psychosis super-spectrum, such that it is difficult to predict who will transition into a more severe state. Furthermore, in samples ascertained on the basis of psychoticism, such as CHR-P and first-episode cohorts, the most common trajectory is one of regression toward the mean, and the abatement of psychoticism.

Development of detachment.

Individual differences in detachment are already apparent by preschool.[160] Detachment has moderate rank-order stability in this period.[191] Likewise, stability is moderate from age 16 to 22 for detachment (r=.51).[165] Detachment in early adolescence predicts subsequent schizophrenia onset.[192] Detachment is primarily a predictor of later negative symptoms.[169–171,193]

While CHR-P status privileges reality distortion, this population is heterogeneous and many experience elevated detachment.[194] In CHR-P, detachment is associated with greater functional and cognitive impairment.[195,196] Schizoid personality disorder is observed in CHR-P[174] and is stable over time,[197] indicating elevated detachment. Indeed, symptoms of detachment are largely explained by stable differences, with detachment being more trait-like than psychoticism.[198]

Detachment remains highly stable through first-episode and into the post-onset period. Among individuals with personality disorders, the 10-year stability of detachment is r=0.82.[185] Among individuals with psychotic disorders,[14,186] symptoms of detachment are nearly twice as stable as symptoms of psychoticism (detachment r=0.38, psychoticism r=0.21).[14] These findings parallel the greater stability for detachment than psychoticism in CHR-P[198] and general youth samples[165] discussed above. Mean-levels of detachment, like psychoticism, are largely flat in the 10–20 years following first onset.[187,188] In sum, the detachment spectrum emerges in childhood, with early individual differences predicting later development of more severe manifestations of the spectrum. Among those with psychotic disorders, detachment is remarkably stable into late adulthood.

Importantly, psychoticism and detachment develop largely independently with minimal (r<0.12) cross-lagged correlations between them.[165] Both traits also predict future internalizing and externalizing problems, but these effects are weaker indicating psychoticism and detachment are relatively specific risk factors for psychotic disorders.[162,164,167,171] Among those with psychotic disorders, the two spectra evolve largely independently.[199,200] Autocorrelations within spectra are much higher than lagged correlations between spectra (r=0.08).[14] In sum, the low magnitude of cross-lagged correlations, relative to auto-correlations, supports psychoticism and detachment as independent spectra with unique contributions to the psychosis superspectrum. Individuals largely progress along the spectrum (or spectra) on which they showed an initial elevation.

Development of cognitive impairment.

Neurodevelopmental evidence suggests cognitive trajectories among those described by the psychosis superspectrum are perturbed in early adolescence, if not childhood. However, the neurodevelopmental theory of psychosis is the subject of considerable interest and debate.[201–203] The evidence is inconclusive, and limited by the lack of longitudinal data on less severe manifestations of these spectra, but some inferences can be drawn by comparing neurodevelopment in healthy, CHR-P, and psychosis cohorts.

Conceptualizing schizophrenia as a neurodevelopmental disorder implies cognitive development is consistently deficient, lagging, or declining among individuals who go

on to develop both psychoticism and detachment. Some data suggest individuals who are later diagnosed with schizophrenia have slowed cognitive development in childhood, consistent with the neurodevelopmental hypothesis.[204] However, cognitive trajectories are best described relative to psychosis onset, rather than chronological age.[205] When described relative to psychosis onset, cognitive development is normal until 14 years before psychosis onset.[205] Consequentially, individuals who experience psychosis onset in their early 20s may have already begun to experience cognitive decline at the chronological ages described by Reichenberg et al.[204] Furthermore, while individuals who go on to develop schizophrenia may have lower cognitive abilities than controls, in childhood future cases seem indistinguishable from their unaffected siblings.[206] This implies that childhood cognitive deficits perhaps are not risk factors for psychosis beyond a general familial liability. When measured relative to psychosis onset, cognitive development among individuals with psychotic disorders is normal, but diverges from controls more than a decade before psychosis onset, grows to about 0.50 standard deviations (SD) below population average by the CHR-P phase. By first onset, cognitive deficits have grown to more than 1.00 SD below average.[59,205,207–209] Cognitive deficits predict transition in CHR-P cohorts, but to a lesser degree than reality distortion.[166]

Structural imaging data indicates neural development largely parallels cognitive function in the psychosis superspectrum. Notably, the structural differences observed in psychotic disorders are observed to a lesser degree in unaffected relatives,[210] and with increasing prominence in clinical high risk individuals,[211] adolescents who have experienced psychotic symptoms,[212] individuals recently diagnosed with schizophrenia, and chronic schizophrenia.[213] Unfortunately, it is not possible to disentangle the effects of severity and illness course in these studies. However, while structural differences have been shown to be associated with genetic liability for psychotic disorders,[214] these links almost entirely explained by individual differences in cognitive function.[210,215] These data and evidence that cognitive decline precedes psychosis onset indicate the centrality of cognitive development to the psychosis superspectrum.

Cognition is quite stable in the general population[216] and in the psychosis superspectrum, meaning long follow-up periods are necessary in order to detect cognitive change in the post-onset period. Short-term follow-up studies of psychotic disorder found greater deficits in schizophrenia than in bipolar disorder but observed little change over time.[58,61,217] However, studies following patients for 10–25 years observed gradual cognitive decline.[57,205,218] Although small on a year-by-year basis, these declined accrue over the illness course, manifesting as a high dementia incidence later in life.[219]

To summarize, cognitive deficits associated with the psychosis super-spectrum emerge more than a decade before the emergence of clinically-significant psychoticism. The rate of cognitive decline is quite slow, but losses accrued over the lifespan are significant. There is some evidence that the rate of cognitive decline accelerates in early adulthood, with many individuals meeting criteria for dementia.

Although there is little data on how strongly cognitive change contributes to psychoticism versus detachment, premorbid cognitive decline is much larger for schizophrenia than

bipolar and other psychotic disorders.[205,220] Cognitive development appears to be unperturbed among those who do not develop detachment symptoms, consistent with a stronger link between cognition and detachment than with psychoticism. More nuanced dynamics of cognition, detachment, and psychoticism and their interplay are poorly understood, in part due to the long time-scales needed to detect cognitive change.

Development of functional impairment.

Functional impairment, like other spectra within the psychotic superspectrum, begins to emerge in childhood. Those who go on to develop psychotic disorders have impaired psychosocial function in childhood, with those later diagnosed with schizophrenia having greater impairment than those diagnosed with affective psychoses.[221,222] Even individuals with subthreshold symptoms of the psychosis superspectrum experience impairment. In the general population, the full range of reality distortion, from subtle illusions to well-formed hallucinations, is associated with psychosocial impairment in a dose-dependent fashion.[223] Real-world functioning is significantly impaired in CHR-P,[224] and psychosocial impairment predicts transition, although to a lesser degree than reality distortion.[166]

In the post-onset period, functional impairment tends to be stable over time,[188,221,225] with an apparent association between the burden of detachment and greater functional impairment. This is reflected in diagnostic data, as recovery rates are persistently lower (20 to 30%) in schizophrenia than in affective psychoses (85%).[72,226] Likewise, employment rates are 30% in schizophrenia compared to 58% in affective psychoses.[227] When detachment and psychoticism are measured directly, greater detachment predicts worse functional outcomes even decades later, whereas psychoticism is not predictive.[228,229] In sum, functional impairments associated with the psychosis superspectrum emerge early, and are stable over time. The links between detachment and functional impairment are particularly strong.

Implications of the psychosis-superspectrum for studies of course.

The HiTOP model provides a framework for a transdiagnostic staging model that describes trajectories of psychoticism, detachment, cognition, psychosocial function, and other spectra across the lifespan.[230–232] The superspectrum model may be most useful in childhood and adolescence, as the DSM-5 has no descriptors for the pre-clinical period aside from Attenuated Psychosis Syndrome, in Section III. However, this category privileges psychoticism over other symptom spectra, and does not include individuals with subthreshold symptoms without functional impairment. HiTOP identifies dimensions (Figure 1) for risk assessment prior to psychosis onset in youth. Moreover, repeated assessments can explicate progression from risk to clinical problems or course patterns in treated samples as individual trajectories. Fine-grained, reliable measures are available for such longitudinal tracing and have been validated in children, adolescents, and adults (see companion paper).[45]

The superspectrum model can also aid in the assessment and further evolution of CHR-P models, by expanding these paradigms beyond the transition to frank psychosis.[184,233] First, dimensional conceptualization enables research on symptom exacerbations that have

not reached full psychotic severity, thus expanding the scope beyond transition. Second, constructs in Figure 1 can facilitate research on other clinically-significant outcomes (e.g., worsening detachment, functional deterioration). Multidimensional risk and outcome assessments can provide critical evidence on the heterotypic (pluripotent) versus homotypic continuity between clinical risk and full-blown disorders. For example, psychopathology other than CHR-P also increases psychosis risk (although much less than CHR-P),[54,234] and CHR-P often leads to non-psychotic disorders.[180] This heterotypy may reflect correlations between different spectra, a hypothesis that could be tested within the HiTOP framework. Hence, clinical staging and CHR-P concepts describe common patterns of illness course that, overlaid onto HiTOP dimensions, offer a heuristic guide to treatment decisions. In return, HiTOP offers staging models a multidimensional characterization of stages based on extensive structural and psychometric research. Moreover, profiling at-risk individuals on lower-order dimensions within the two spectra is expected to increase prediction accuracy and specificity.

The psychosis superspectrum also has advantages for describing post-onset course. In diagnostic frameworks, course is typically characterized in terms of remission, the criteria for which combine psychoticism and detachment symptoms.[235] Lower rates of remission in schizophrenia (56%) and schizotypal personality disorder (46%) compared to affective psychosis (79%) are consistent with the higher burden of detachment in these disorders.[72,236] Similarly, definitions of recovery combine psychoticism, detachment, and functional impairment.[237] These traditional operationalizations of course provide useful clinical benchmarks but miss many details. The HiTOP psychosis superspectrum offers advantages over existing operationalizations by specifying remission for each spectrum, and distinguishing functional recovery from symptomatic remission. In addition, dimensional models can capture subtle changes in symptom severity that are missed by dichotomous constructs, because small changes rarely move an individual across a threshold. Topics such as the impact of repeated psychotic episodes on antipsychotic efficacy[238,239] can be studied as interactions of time, treatment, and symptom severity.

The psychosis superspectrum provides a useful framework for studying the course of psychoticism, detachment, cognition, and functional impairment. However, it does not yet include temporal patterns themselves. Patterns such as psychosis recurrence or co-occurrence between psychosis and mania over time have major implications for treatment and prognosis.[240,241] Traditional nosologies attempt to capture this information using heuristic categories, such as course specifiers (e.g., first episode vs. multiple episodes) and diagnoses (e.g., bipolar disorder with psychosis vs. schizoaffective disorder vs. schizophrenia). Research is ongoing to identify empirical and quantitative course characteristics.[242–244] For example, recurrence frequency can be represented by within-person symptom variability of co-occurrence by within-person symptoms correlations. The number of potential quantitative characteristics is large, including intercept (propensity to experience symptoms), slope of the trajectory (direction and rate of change), autoregressive effects (symptom stability), cross-lagged effects (shifts in presentation), and many others. The literature on the quantitative characteristics of course is growing, but to incorporate these features into HiTOP, structural analyses needed to consider course-based constructs together with existing HiTOP constructs, and explicate relations between them. Such

integrative studies are rare,[245] but as science advances it will become possible to include course features in the superspectrum model. At present, the model captures the distinction between symptoms and traits (i.e., current acute state and persistent problems). This distinction offers only a limited characterization of course but already has proven to increase utility of the model beyond symptoms alone.[246]

Conclusions

The HiTOP psychosis superspectrum, a hierarchical, transdiagnostic model of psychosis-related psychopathology, shows promise as an alternative to DSM and ICD diagnoses. Derived through construct validation,[28] the psychosis superspectrum captures both the comorbidity and heterogeneity through a hierarchical structure, with constructs reflecting varying degrees of breadth versus specificity. The model accounts for heterogeneity by distinguishing psychoticism—which includes hallucinations, delusions, disorganization, and maladaptive traits such as unusual beliefs and peculiarity—from detachment—which includes avolition, inexpressivity, and traits such as anhedonia and social withdrawal. Auxiliary domains include cognitive and functional deficits, completing the profile of psychotic disorders and related psychopathologies.

The psychosis superspectrum's higher-order structure, including psychoticism, detachment, and cognitive deficits, mirrors the structure of genetic risk described by behavioral and molecular genetic research. Although genetic data on narrower components of the superspectrum are less common, existing evidence hints at the potential for identifying unique genetic liabilities underlying traits and symptom components. The psychosis superspectrum also informs the understanding of environmental and societal risk factors associated with psychotic disorders, as established risks are more strongly associated with psychoticism than detachment. Together, the interaction of genetic risk and environmental exposures may increase risk for schizophrenia spectrum disorders,[159] although these findings need to be replicated. A HiTOP approach to quantifying genetic risk and environmental stressors may facilitate more precise, powerful tests of the diathesis-stress model.

The HiTOP model's dimensional nature is particularly useful for studies of the development of psychosis, facilitating models of developmental trajectories leading to clinical problems. Transdiagnostic elements facilitate the comprehensive investigation of outcomes of at-risk states, beyond the onset of frank psychosis. While longitudinal studies of psychotic disorders have illustrated the course of psychoticism and detachment, as well as cognition and functioning, more research is needed on the longitudinal course of maladaptive traits and subthreshold symptoms.

The HiTOP model is intended to reflect currently available structural and validation evidence. As such, it is continually under development. The provisional status of numerous elements, including mania, dissociation, cognitive deficits, and functional impairment, are notable limitations. The model also is limited in how it captures illness course. Efforts to address these limitations are ongoing.

The companion paper completes this review by considering data on neurobiology, treatment response, clinical utility, and measurement.[45]

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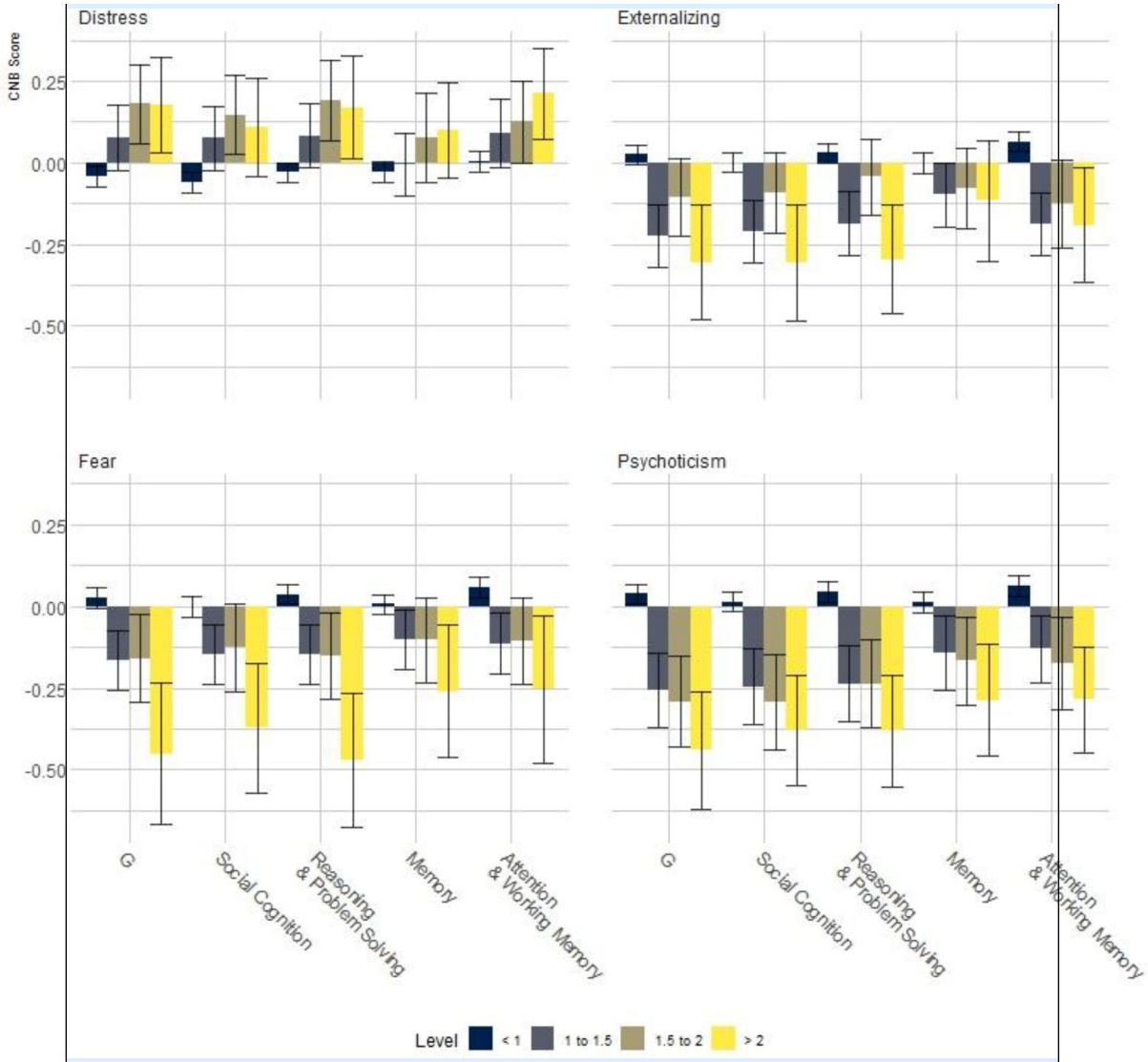
Box 1

To illustrate application of HiTOP spectra to explication of connections between neurocognition and psychopathology, we leveraged the Philadelphia Neurodevelopmental Cohort (PNC). The PNC is a community sample of nearly 10,000 genotyped youth who were phenotyped in 2009–2011 as part of an ARRA Grand Opportunity (GO) project.[248] Participants received a thorough clinical assessment using the GOASSESS, an adaptation of the K-SADS covering major DSM disorders. They also received a neurocognitive assessment, the Penn Computerized Neurocognitive Battery (PennCNB) that included 14 tests, providing measures of accuracy and speed on major neurocognitive domains.[249]

Psychoticism, externalizing, and two internalizing subdimensions (distress and fear) were linked to four cognitive abilities assessed by the PennCNB: general intelligence, social cognition, reasoning and problem solving, memory, and attention.[250] A bifactor model was used to remove variance attributable to the p-factor from spectra, to focus on specific psychopathology-cognition links. The associations between HiTOP spectra and cognitive traits are reported in the Figure below.



Box Figure: Cognition by Spectrum

As can be seen in the Figure, the 200 males and 150 females in the highest percentile of psychoticism showed cognitive deficits with a moderate effect size (d>0.40), consistent with the magnitude of cognitive deficits observed in CHR-P and prodromal cohorts.[251] The greatest deficits were observed in G, or the general cognitive factor, but deficits of similar magnitude were observed in social cognition, and reasoning & problem solving.

The effect sizes for externalizing are considerably smaller, but emerge at lower levels of severity. In contrast to all other psychopathology domains, the distress dimension was associated with better than average performance. This “paradoxical” effect of distress being positively associated with performance is likely due to these analyses controlling for the p-factor. In other words, psychopathology in general is associated with worse cognitive functioning, but when this effect is controlled, distress is associated with better functioning than psychosis or disinhibition.

The results presented here are sparse and designed to illustrate an approach for linking clinical with neurocognitive domains. We only show data concerning psychoticism, and not detachment. In addition, there could be scientifically and clinically meaningful links between specific traits and symptom components and cognitive abilities. There are other neurocognitive domains of high potential relevance to psychopathology dimension, like reward processing, or meta-cognitive traits such as insight, which may be informative.

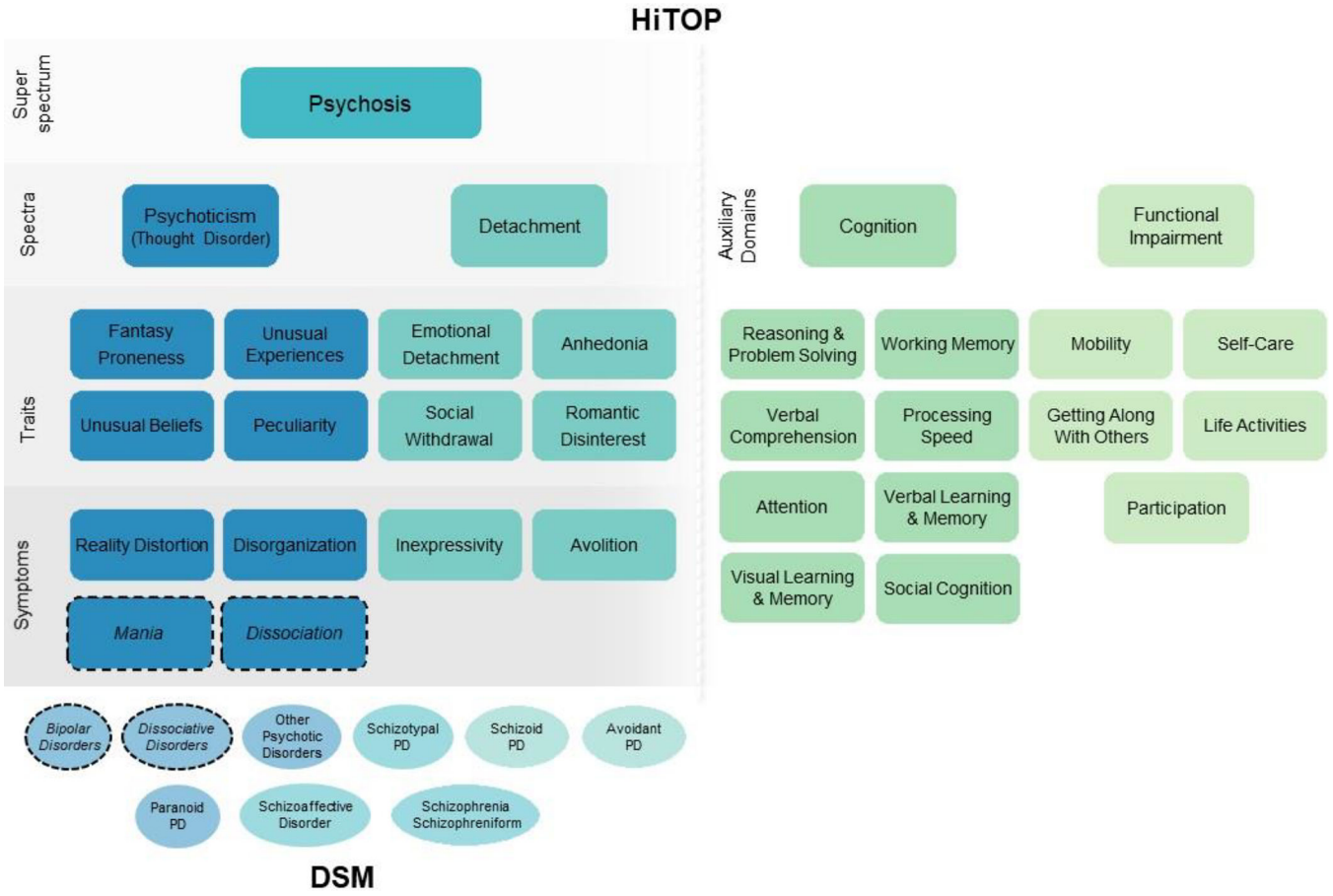


Figure 1. HiTOP model of psychosis superspectrum

Note. Dashed circles indicate mania and dissociation are include in the model provisionally, because evidence supporting their inclusion is limited. Thought disorder is given in parentheses because it is the term currently used in HiTOP for the psychoticism spectrum.

Table 1.

Definitions of constructs within the psychosis superspectrum

Construct	Definition
Psychosis superspectrum	General individual difference in cognition and behavior that ranges from conventional and goal-oriented (low end) to bizarre and apathetic (high end).
Psychoticism (thought disorder) spectrum	General individual difference in perception, cognition, and behavior that ranges from conventional and uncreative (low end) to disconnected from reality (high end).
Fantasy Proneness trait	Tendency to fantasize, daydream, and become fully engrossed in one's thoughts and experiences, sometimes becoming distracted and losing sight of reality.
Unusual Experiences trait	Tendency to experience perceptions that do not correspond to reality or impaired perception of self, including anomalous self-experiences, derealization, depersonalization, illusions, and frank hallucinations.
Unusual Beliefs trait	Tendency to hold unfounded and irrational thoughts, beliefs, and ideas about the world as well as frank delusions. This includes beliefs about the powers of oneself, others, and objects to control and influence others and the physical world.
Peculiarity trait	Tendency to exhibit behavior, speech, appearance, and mannerisms that are unusual, eccentric, or bizarre in person's culture.
Reality Distortion component	Acute experience of illusions, hallucinations, irrational thoughts, or frank delusions.
Disorganization component	Acute unusual or bizarre behavior, speech, mannerisms, or appearance. This includes formal thought disorder (i.e., impaired capacity to sustain coherent discourse).
Mania component	Acute euphoria and excessive goal-directed activity; hyperactive cognition and speech; overconfidence and grandiosity that may result in recklessness.
Dissociation component	Acute experience of depersonalization, derealization, dissociative amnesia, reduced awareness of the surroundings, or trance states
Detachment spectrum	General individual difference in volition, sociability, and affective expression that ranges from goal-oriented, sociable, and expressive behavior (low end) to apathy, disinterest in people, and blunted affect (high end)
Emotional Detachment trait	Tendency to be emotionally distant and reserved, impaired ability to experience, describe, and express feelings.
Anhedonia trait	Tendency to experience low levels of positive emotions (e.g., joy, confidence, alertness), energy, and interest in activities.
Social Withdrawal trait	Tendency to avoid interpersonal interactions or not initiate social contact, reticence in social situations, and a preference for being alone.
Romantic Disinterest trait	Tendency to lack of interest in, desire for, and enjoyment of sex, eroticism, and interpersonal intimacy.
Inexpressivity component	Acute deficit in vocal and facial expressions of affect, expressive gestures and eye contact, and alogia (e.g., poverty of speech, long latency of response)
Avolition component	Acute deficit in initiating or sustaining engagement in social, recreational, or occupational activities; remaining physically inert for long periods of time; deficit in positive emotions and energy; deficit in desire for intimacy or sex.

Note: The definitions were drawn from multiple sources that characterized subsets of these constructs.[12,16,247]