allow practitioners to implement many aspects of the system already.

HiTOP can be used most feasibly in a stepwise manner, beginning with a brief measure of the six spectra. If problems are detected in some spectra, lengthier measures can be administered to characterize dimensions within those domains (while the other domains do not require further assessment). Thus, a HiTOP diagnosis is a patient's profile on relevant dimensions. Although such profiles may include a large number of scales, they are often simpler than traditional manuals, with their hundreds of codes and numerous permutations necessitated by comorbidities[10].

Clinical decisions require cut-offs on dimensions to guide specific actions. The HiTOP consortium aims to develop such cut-offs empirically, and cut-offs based on statistical deviance already exist (e.g., two standard deviations above the mean indicate high severity).

Indeed, HiTOP is a work in progress. Ongoing efforts aim to extend the system to all forms of psychopathology, construct an integrated measure of all HiTOP dimensions, and develop detailed guidance for clinicians using the system. Much more needs to be done, but HiTOP already can be applied in a variety of contexts. At minimum, it provides a framework for conceptualizing research phenotypes and individual patients dimensionally. Ultimately, HiTOP is expected to offer a roadmap for researchers and clinicians that is much more informative than traditional diagnostic systems.

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# Schizotypy, schizotypic psychopathology and schizophrenia

The term schizotypy refers to a latent personality organization that putatively harbors the liability for schizophrenia and can give rise to a variety of schizophrenia-related phenotypic outcomes[1,2].

This personality organization, which is determined by any number of as-yet-unknown schizophrenia-related genetic influences acting against a background of polygenic assets and liabilities as well as impacts from the environment (e.g., stressors, epigenetic inputs), can manifest itself variously at the phenotypic level, ranging from clinically diagnosable schizophrenia through pathological personality manifestations (e.g., schizotypal, paranoid, avoidant and schizoid personality disorders) to subtle, sub-clinical psychotic-like phenomenology (e.g., perceptual aberrations, magical ideation, referential thinking, interpersonal aversiveness).

Schizotypy may also manifest itself in an imperceptible manner, undetectable by the unaided naked eye, through deviance on endophenotypes that have established valid relations with schizophrenia.

Moreover, schizotypy as a latent construct (personality organization) is centrally embedded in a diathesis-stressor theoretical model that has considerable utility as an organizing framework for the study of schizophrenia, schizophrenia-related psychopathology (e.g., delusional disorder, psychosis not otherwise specified, schizotypal, paranoid and other related personality disorders) as well as putative schizophrenia endophenotypes, a view I have advocated for several decades[3-6].

Note, the term schizotypy is not restricted to describe only those clinical manifestations that are associated with schizotypal personality disorder[2,5,6]. Nor is the term reserved to indicate a methodological preference, e.g. for self-report psychometric assessments. Rather, schizotypy can be assessed using a variety of approaches such as interviews, psychometric inventories, familial risk and/or laboratory measures. Schizotypic persons may indeed display some of the phenomenology associated with schizotypal personality disorder, but they may also show other features[6-8].

There is a long history of describing clinical states bearing the imprint of schizotypy and an implicit connection to schizophrenia liability, including observations by Kraepelin, Bleuler, Rado, Meehl, Gottesman and myself. It has been argued that a clear demarcation in an underlying schizophrenia liability continuum (e.g., a pronounced threshold effect or discontinuity) is required to explain the emergence of schizotypic indicators in psychological functioning. An alternative position regarding schizotypy holds that it is a dimension of normal personality, not necessarily connected to schizophrenia liability, and representing something of a "healthy" personality factor. However, observers of schizophrenia and schizotypic psychopathology, in the main, do not view schizotypy as benign or reflective of healthy psychological adjustment.

Non-psychotic schizotypic states (defined using clinical, laboratory and/or familial risk) have been associated with a wide range of findings, including sustained attention deficits,

working memory deficits, smooth pursuit eye movement dysfunction, schizophrenia-related psychometric deviance on the Minnesota Multiphasic Personality Inventory (MMPI), executive functioning deficits, dysfunctional anti-saccade performance, subtle formal thought disorder, clinical schizotypal and paranoid personality features, schizophrenia-related social cognition deficits, exteroceptive and proprioceptive somatosensory deficits, psychomotor abnormalities, and candidate polymorphisms (e.g., ZNF804A, Val158Met-COMT, neuregulin-1). That schizotypic persons manifest such a panorama of deficits, similar in nature albeit less in degree to those seen in schizophrenia, argues for a connection or common underlying construct for conditions defined phenotypically (i.e., schizotypic subjects vs. schizophrenia-affected subjects).

An area of continued speculation concerns the underlying structure of schizotypy and the precise nature of the variation expressed in that latent construct. Considerable statistical evidence, using a variety of latent structure methods, points to the existence of possible underlying discontinuities or severe threshold effects in schizotypy, and work in this area continues. Such evidence stimulates the caveat, to wit, that the use of continuous measures to assess phenotypic manifestations of schizotypy does not *ipso facto* mean that the underlying (or latent) schizotypy construct is fully quantitative or uniformly graded by degree.

The course and clinical outcome for those designated as harboring schizotypy remains an area of active inquiry. It is entirely conceivable that many individuals possessing schizotypy may traverse the life course escaping psychotic illness as well as other diagnosable schizotypic manifestations. The expectation that some people validly at risk for schizophrenia may never manifest the illness is well established in the reality of discordant monozygotic twins, in which one twin is affected by schizophrenia and the co-twin is not psychotic (perhaps not even diagnosable as having a non-psychotic, but detectable, clinical schizotypic condition like schizotypal or paranoid personality disorder).

Individuals that achieve elevated scores on psychometric measures of schizotypy have been shown to be at increased risk for schizophrenia and schizophrenia-related psychoses later in life, as well as a variety of other related outcomes. Such individuals also display poorer psychosocial functioning, lower rates of marriage, increased use of psychiatric medications, and increased utilization of psychiatric services[2]. It is entirely conceivable that many individuals designated as "prodromal" for schizophrenia, but who do not convert to schizophrenia (which is 60-70% of such subjects), are in fact harboring schizotypy and will, even if not psychotic, show impairments across the life span, perhaps adopting an eccentric or odd manner of personality functioning.

The schizotypy model has helped to adjust the boundaries of schizophrenia phenotype in the DSM-5 (e.g., schizotypal pathology is now included with schizophrenia). Furthermore, illuminating the nature of schizotypy may aid in unraveling the current puzzle of the very low conversion to schizophrenia rates seen in "prodromal" schizophrenia research[9].

Finally, I have argued that the schizotypy framework may be useful in understanding *configurations* (rather than simple additive summation) of genes relevant to schizophrenia variants[2], an idea that is beginning to gain traction. There is no doubt that incorporation of schizotypy indicators into genomic studies of schizophrenia increase their statistical power.

The advantages of a cleaner unit of analysis (the schizotype), free from the effects of medication, institutionalization and neurocognitive decline, are axiomatic. However, the understanding (and misunderstanding) of the schizotypy model as well as alternative approaches to the construct require vigilance, in order to ensure that the approach continues to yield the fruit that it can.

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# The value of polygenic analyses in psychiatry

The last decade of genetics research in psychiatry (and in other fields) has been dominated by genome-wide association (GWA) studies, in which common variants across the genome are tested for association with a trait or disorder. These studies have shown that polygenicity is the rule, i.e., psychiatric disorders are influenced by many (likely thousands of) genetic variants, each with a small effect[1].

This is best illustrated by the flagship GWA meta-analysis on schizophrenia, which is the first disorder that has achieved the sample size needed to detect the effect sizes that have been dealt by nature's hand. By analysing 37,000 cases and 113,000 controls, 108 associated regions were identified[2]. However, the significant variants together only explained 3.4% on the liability scale for schizophrenia, indicating there are many more vari-