Using the Hierarchical Taxonomy of Psychopathology (HiTOP) for precision psychiatry

Progress in developing effective psychiatric interventions has been slow, in part because of the heterogeneity of diagnostic categories[1-3]. Within a single diagnosis, specific treatments are often helpful for some patients but not others. This has led psychiatry to an interest in individual differences and to the rise of *precision psychiatry*[4].

Drawing on the more general concept of precision medicine, a central premise of precision psychiatry is that knowing the specifics of an individual's biological makeup will facilitate intervention more effectively than knowing only a diagnosis. However, identifying robust links between neurobiological variables and psychiatric problems has proved difficult, partly due to the limitations of diagnostic categories.

A large body of evidence indicates that mental disorders are not discrete categorical biological entities but instead exist on continuous spectra across the general population[3]. Physical medicine explicitly recognizes that the designation of a threshold for diagnosis (e.g., hypertension) often does not indicate a qualitative boundary, because many biological variables (e.g., blood pressure) are fundamentally dimensional. Here, we argue that precision psychiatry can benefit from adopting a similar dimensional approach, and that the Hierarchical Taxonomy of Psychopathology (HiTOP) offers an excellent framework for doing so, addressing several key limitations of official nosologies.

HiTOP is a dimensional model developed by a large consortium of researchers on the basis of statistical analysis of the covariation among symptoms and diagnoses[3,5,6]. This quantitative approach is helpful, because patterns of covariance among symptoms often do not match diagnostic criterion sets. In other words, symptoms do not actually tend to cluster in the patterns indicated by official nosologies[2,3]. This means that problems with existing diagnoses cannot be remedied simply by transforming them directly from categorical to dimensional, maintaining the same symptom criteria and aggregating those to indicate a spectrum for each disorder.

Instead, to match actual covariance patterns, HiTOP reorganizes symptoms into multiple dimensions across hierarchical levels, with the core level containing six broad spectra: internalizing, antagonistic externalizing, disinhibited externalizing, thought disorder, detachment, and somatoform. Above the spectra are superspectra including the general factor of psychopathology (or p factor), which represents the shared likelihood of all mental disorders, and below the spectra are various subfactors, and below those are many specific symptom dimensions[3].

HiTOP provides a degree of precision in characterizing clinical phenomena similar to what the Research Domain Criteria (RDoC) aims to provide at the neurobiological level, thereby rendering the two systems complementary[5,6]. HiTOP offers assessments that are effective targets of neuroscientific research[5]. Both HiTOP and RDoC are not only dimensional and transdiagnostic, but also hierarchical, encompassing broad constructs representing extensive patterns of covariation and narrower constructs nested within them. A thorough understanding of the neurobiology of psychopathology will require identifying neural correlates of broad spectra (e.g., internalizing) to explain symptom coherence, as well as distinct correlates of specific symptoms (e.g., anhedonia) that account for their differentiation at lower levels of the hierarchy[7].

Precision psychiatry can and should work on both sides of the equation, delivering precision in clinical description by using a system such as HiTOP, while at the same time delivering precision in neurobiological characterization[6]. One of the core tenets of precision psychiatry is to use data-driven classifications[4]. Such work is already being conducted on the neurobiological side, and this is exactly what HiTOP provides for clinical description, classifying symptoms into broader spectra based on analysis of covariance. Precision psychiatry will be

most likely to identify effective treatments based on characterizing individual patients in terms of their full symptom profile, in conjunction with various biological assessments.

In research aiming at precision psychiatry, an increasingly common approach to dealing with heterogeneity is to identify subtypes within existing diagnoses based on neurobiological variables[1,8]. Despite the potential value of employing cutting-edge neuroscientific methods to identify distinctions within diagnoses, this subtyping approach has two important limitations.

First, it starts from categories that are not scientifically valid. If a diagnosis such as major depressive disorder or schizophrenia is already known to include people with very different symptoms and to exclude people with meaningfully similar symptoms, searching for precision within that diagnosis will yield incomplete information. Studying a broader treatment-seeking population would be more effective.

Second, the subtyping approach generates putative categories (i.e., subtypes) where the available evidence suggests that categories are unlikely to exist in nature. Like symptoms, variables derived from human neuroimaging are typically distributed dimensionally without clear demarcations that would indicate categorical entities. This fact may explain why neurobiological subtyping has often failed to replicate and why its division of individuals within a given sample depends heavily on the neurobiological variables analyzed[8].

A solution to both of these challenges is to relate neurobiological variables to transdiagnostic symptom dimensions in more inclusive samples, such that precision comes from linking a reasonably comprehensive hierarchy of symptom dimensions to a broad array of neurobiological variables.

HiTOP is a good framework for symptom assessment in part because its dimensions have been found to explain more variance in neural correlates than diagnoses do, even in the same sample[9]. A recent systematic review shows both the increasing use of dimensional approaches in clinical neuroscience and the promise of HiTOP for the field[5]. This review of 164 neuroimaging studies with sample sizes ≥194 identified ten replicated findings (though with additional failures to replicate in three cases) at five different levels of the dimensional hierarchy. These levels ranged from associations of the p factor with reduced brain volume, to associations of the thought disorder spectrum with reduced frontotemporal functional connectivity, to associations of depressed affect (a specific symptom dimension) with reduced amplitude of brain responses to reward. As more such associations are identified, they will provide a key ingredient to the biological side of precision psychiatry, complementing symptom assessments with insights into potential neural mechanisms.

The dimensional approach is a crucial advance for clinical neuroscience and precision psychiatry. However, within this approach, challenges arise when researchers measure only one or a small range of symptom dimensions. Without a sufficiently comprehensive set of dimensions, it is difficult to determine whether a finding of association between a neural variable and a particular symptom dimension is truly specific to that dimension, or is instead more strongly associated with a different dimension that shares some variance with the first dimension or with a broader construct that subsumes that dimension.

HiTOP offers a solution. With an assessment covering all of the HiTOP spectra, one can identify not only what symptoms a given neural variable predicts, but also what symptoms it does not predict. In other words, one can establish discriminant validity. This means identifying not only the relevant dimension, but also the level of the hierarchy to which a variable relates.

Once an evidence base has accumulated in which we know with confidence what level and dimension many neurobiological variables are linked to, precision psychiatry will be better positioned to achieve its full potential. Accurate clinical phenotyping is necessary for effectively identifying the biological basis of individual differences, and HiTOP can provide it, offering an accelerator for precision psychiatry.

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