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On the Hierarchical Organization of Psychopathology and Optimizing Symptom Assessments for Biological Psychiatry

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Karl Menninger might be pleased by current thinking about models of psychopathology. He saw a pendulum historically oscillating between categorical and dimensional views of mental illness, and personally advocated a dimensional, and even a unitary approach to mental disorders (1). Little did he know that the Diagnostic and Statistical Manual in its third edition (DSM-III) would soon reify categorical boundaries for the next generation. Today, he could open his copy of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, and see that the pendulum is now accelerating in the dimensional direction, with nonspecific forms of psychopathology back in the spotlight a half-century later!

We are indebted to Zald and Lahey for their critical analysis and accessible proposals about the implications of recent work on the hierarchical structure of psychopathology(2). They articulate beautifully recent findings that have revealed, across diverse samples spanning children and adults, dimensions of internalizing and externalizing symptoms superimposed on a backdrop of generalized psychopathology, echoing the unidimensional proposals of Menninger and Llopis(3). They productively relate this body of work to the emergence of the National Institute of Mental Health (NIMH) Research Domains Criteria (RDoC) initiative. Among the challenges, Zald and Lahey are particularly interested in elucidating transdiagnostic mechanisms of psychopathology. They focus on a “hierarchical structural” approach that integrates: (a) the narrow symptom approach; (b) the broad dimensional approach; and (c) the “functional constructs” approach (which focuses on functional processes other than symptoms or diagnoses). The hierarchy they identify spans, from lowest to highest:

- Individual symptoms;
- First-order dimensions (based on correlations among individual symptoms);

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- Second-order dimensions (based on correlations among subsets of first-order dimensions);
- General factor of psychopathology (based on correlations among almost all symptoms).

There are multiple implications of the hierarchical approach. The most general assertion is that that "... the neural correlates of psychopathology ... differ in breadth in direct relation to the level of the structural hierarchy of psychopathology. Narrower neural correlates may be expected when symptoms are limited to a single dimension. By contrast, broad neural features, such as those captured by whole brain metrics, will be more saliently associated with higher order factors of psychopathology" (page 14). For example, they suggest that motivational anhedonia is an individual symptom (distinct from "consummatory anhedonia") linked to specific neurocircuitry involving dopaminergic transmission in the ventral striatum. They complement this with evidence about the high degree of genetic variance that is shared at the level of higher-order dimensions (e.g., 66% of genetic variance is accounted for by internalizing and externalizing dimensions in children and adolescents (4).

Zald and Lahey further highlight multiple advantages of the hierarchical approach. One key asset is that higher dimensions can help overcome problems imposed by high correlations among individual symptoms or lower-level dimensions, making it hard to tease apart their influence on external variables. The higher-order variables possess higher reliability, and all other things being equal, higher validity in their correlations with external variables. Another major advantage is that by identifying neural substrates that "non-specifically" contribute to psychopathology, this will facilitate the study of mechanisms that are more specific to single dimensions and subsets of symptoms. They offer an example from the work of Shanmugan and colleagues. This example is important in showing how the bifactor model helps reveal more specific patterns of brain-behavior associations after controlling for a general factor.

These opportunities are exciting and the overall framework is elegant and appealing. Zald and Lahey offer a clear roadmap to help guide research. At the same time, leveraging the hierarchical structure hypothesis will confront challenges and the hypothesis may benefit from extensions. A few ideas include:

- Notwithstanding the example provided (motivational anhedonia), there remain few findings linking specific symptoms of psychopathology, however narrowly defined, to responsible neural substrates. Zald and Lahey acknowledge that many symptoms do not relate clearly even to functional constructs, much less neural circuitry. The ability to link circuit-level measures to clinically observed symptoms remains an empirical question. We might ask if the sparsity of positive results reflects need for:
 - Better definitions of symptoms;
 - Better definitions of neural circuits; or

- Better models, acknowledging that associations may not be found between these levels of analysis because they are separated by too many unknown or unspecified mediating variables.

A relevant example comes from the NIMH Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia Consortium(5). They found that conventional “multifactorial” neuropsychological tests correlated better with symptoms and real world outcomes than did more “specific” cognitive measures, which had associations with neural circuitry. We may need to consider seriously the possibility that many clinically observed (most?) symptoms are at a level of abstraction such that no statistical parsing of their co-occurrence will render them more neatly associated with underlying circuit function.

- Zald and Lahey suggest “... that both dimension-specific and broadly pleiotropic genetic influences operate at varying levels of the structural hierarchy...” (page 9), but so far the evidence favors broad influences over dimension-specific. Zald and Lahey indicate this may be due the former (broad) associations being more robust than the latter (specific) associations, but as stated above, what if the more specific associations are so small that efforts are better dedicated to more tractable problems?
- The bifactor model presented by Zald and Lahey has many advantages, but remains rooted in a psychometric model, which assumes that observable symptoms arise from latent constructs. What if the first-order factor structure is in part an artifact of cross-sectional measurement that conflates many different causal paths to the same pattern of symptom co-occurrence? Might clearer links to underlying neural circuits be identified from unique longitudinal trajectories of symptoms as these unfold? Can we find better causal models to explain the emergence of symptoms(6)?
- Zald and Lahey suggest the importance of broadening symptom assessment beyond what is now used to generate diagnoses, given that crucial information may be missing. This will be a hard sell for big studies, when each added question can add weeks of effort (e.g., one 10-second question in 100,000 people, increases study time by about 35 days for a full-time interviewer!). Thus, it will be important to do more efficient modeling of both dimensions and categories and determine what key questions we need to get all the useful variation out of symptom assessments. This tension between comprehensive assessment (to assure we are not missing critical data) and efficient assessment (to enable adequately powered genetic studies) has never been more poignant. How do we identify the “sweet spot” that maximizes collection of necessary phenotype data and minimizes time? It is exciting, for example, that computerized adaptive test (CAT) methods can measure depression either categorically or dimensionally with high precision using only 6 to 10 questions each (7, 8). But these methods are validated with respect to current diagnostic or dimensional views of what is the “latent trait”, when the biologically relevant

observations may be about other symptoms, or removed from symptoms altogether. Can we start with CAT approaches to define “legacy” constructs (like the diagnoses that have been the basis of virtually all case-control studies so far, and key dimensions such as internalizing and externalizing behavior), and augment these with items that will flesh out the phenotypic space that may be missed? Can we develop strategies to define the “missing” items we need – in other words, can we identify phenotypic “dark matter”? Kendler recently brought attention to phenomenological concepts that were prominent in earlier characterization of depression and schizophrenia, but largely dropped during the DSM development process(9, 10). Might similar approaches serve as a starting point to develop efficient questions that branch into these spaces as needed?

- The implications of the hierarchical model for RDoC also merit further consideration. Zald and Lahey suggest that “functional constructs” may mediate the relations between brain and symptoms, but is this true? This formulation does not seem to be explicit in the current formulation of the RDoC matrix, and this prompts the question: should it be explicit? Zald and Lahey state: “...As such, we need to consider which functional constructs or combination of constructs exert influences at higher levels of the hierarchy” (page 14). This again raises the question: Is the level of symptoms so far removed from neural substrates that our efforts to link these to RDoC functional constructs is suboptimal? It may be valuable, rather than seeing this as a black or white issue, to consider a subtle re-phrasing of the Zald and Lahey recommendation: *before believe something more specific we should rule out more general associations*. This follows the general logic of the hierarchical model, and may help afford us some protection against false positive discoveries that may arise from exploring the universe of symptoms.

Zald and Lahey have done an outstanding job bringing to our attention the implications of findings about the hierarchical structure of psychopathology. We now have the opportunity to test the validity of the hypotheses they raise and we hope advance the understanding of the basic brain mechanisms underlying dimensions of mental function in both health and illness.

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