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“If the Shoe Fits ...”: The Hierarchical Structure of Psychopathology and Psychiatric Neuroimaging

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Heterogeneous diagnostic categories, comorbidity, and longitudinal shifts in diagnosis pose fundamental challenges in unraveling the biology of mental illness and developing new treatments. In recent decades, a new perspective on these diagnostic quandaries has taken root. According to this view, these challenges should not be dismissed as confounds to a tidier psychiatric nosology but should be taken instead as a reflection of the higher order structure of psychopathology (1,2). In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Zald and Lahey (3) argue that adoption of a data-driven, hierarchical model of psychopathology, based on well-established patterns of correlations among symptoms and traits, may provide better traction than traditional diagnoses for psychiatric neuroimaging research and other biological discovery.

In this hierarchical model, first-order dimensions are defined by the strongest associations among symptoms and often resemble traditional diagnoses. Correlations among first-order dimensions define higher-order dimensions (e.g., internalizing and externalizing psychopathology), while correlations at this higher-order level define a general factor of psychopathology [or “p factor” (1)]. The hierarchical model of psychopathology is a conceptual sibling to the more familiar hierarchical model of cognition (4). In parallel with the psychopathology model, the cognition model posits that a broad, second-order general cognitive ability factor (the g factor, which is similar to IQ) accounts for much of the variation in performance on dozens of narrow cognitive abilities (e.g., memory for word lists) through its influence on intermediate-breadth, first-order dimensions representing separable performance domains (e.g., verbal memory, attention). As the g factor reflects lower-to-higher broad cognitive ability, so the p factor is hypothesized to account for substantial variation in the overall severity of psychopathology (1,3).

Zald and Lahey (3) are particularly interested in the implications of the hierarchical model of psychopathology for mental illness etiology. They hypothesize that the observed correlational patterns in symptoms reflect a parallel, underlying etiological hierarchy: from first-order–specific effects of biology on behavior to increasingly generalized etiological influences. At the level of the p factor, nonspecific etiological factors (e.g., genetics, childhood adversity) increase risk for all first-order dimensions of psychopathology to

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varying degrees. Zald and Lahey propose that causal influences may operate simultaneously in individuals at different levels of the hierarchy. Different combinations of influences may produce the same diagnosis, while a given set of influences may yield quite different outcomes across individuals. Moderating factors, such as sex and cognitive ability, also influence the emergence and form of psychopathology (5). In the end, the full framework anticipates a complex mix of broad, nonspecific etiologies interacting with one another, with more specific influences at lower levels of the hierarchy, and with moderating factors.

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Support for a hierarchical model of etiology is available from genetic and environmental risk factor studies, including twin, family, and molecular studies [reviewed in (5)]. An important conclusion from such studies is that the variance accounted for by specific etiological factors may be modest compared with variance accounted for by higher-order factors (3). In another study from Lahey et al. (6), for example, two-thirds of genetic variance in first-order symptom dimensions was explained by higher-order internalizing, externalizing, or general psychopathology dimensions. Again, such findings are in parallel with family and molecular studies in cognition, which suggest that most etiological influences on cognitive performance are general in their effects [reviewed in (7)].

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For Zald and Lahey (3), the model has clear implications for psychiatric neuroimaging research and clinical neuroscience. One implication that many will endorse is that studying “one categorically defined mental disorder at a time” (5) is likely to suggest misleadingly specific brain-behavior mappings, actually slowing progress in teasing apart mechanistic heterogeneity. Zald and Lahey point to the National Institute of Mental Health Research Domain Criteria initiative as one corrective step. The Research Domain Criteria initiative directs attention toward functional constructs (e.g., reward processing) and away from categorical diagnoses (8). Research Domain Criteria constructs are expected to be relevant to multiple diagnoses, and the initiative encourages cross-diagnostic research. This emphasis on researching across diagnoses is especially close to the heart of Zald and Lahey’s hierarchical framework (5). They argue that cross-diagnostic sampling will help the field avoid pseudospecific etiology/diagnosis associations and enable researchers to test the generality or specificity of etiological effects across diagnoses. In other words, these designs permit researchers to determine the level of the hierarchy of psychopathology through which different etiological influences have their impact. In addition to cross-diagnosis sampling, the authors also ask researchers to welcome comorbidity rather than focusing on prototypical cases within various diagnostic categories and, generally, to apply no or minimal diagnostic inclusion criteria. Zald and Lahey argue that these steps will result in more demographically representative samples and allow modeling of the neural correlates of nonspecific, higher-order factors of psychopathology simultaneously with those more specific to first-order (i.e., diagnosis-level) dimensions.

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While this framework may succeed in accommodating various stubborn empirical findings, Zald and Lahey (3) recognize that testing it will be resource intensive and raise challenging practical issues. Multisite planning and coordination likely will be required to recruit large cross-diagnostic samples and obtain the needed volume of high-quality and consistent neuroimaging data. Even in quite large cross-diagnostic samples, it will prove difficult to avoid confounds, such as differing proportions of various psychopathologies across samples.

Other necessary methodological refinements would go well beyond sampling strategies. For example, it will be possible to detect higher-order influences on psycho-pathology in such samples only if symptom assessments are also comprehensive and inclusive. These assessments will have to avoid commonly employed short-cuts, such as for-going the rating of less diagnostically discriminating symptoms (e.g., negative affect), which might be relevant to higher-order dimensions of psychopathology, or using algorithms in individual assessments that skip past less prominent symptomatic themes and comorbidities to derive single, categorical diagnoses. Selection of neuroimaging paradigms and analytical approaches will be equally challenging. Zald and Lahey (3) suggest, for example, that task-based functional magnetic resonance imaging paradigms may be best suited for identifying narrow constructs at lower levels of the hierarchy, whereas whole-brain metrics might have greater explanatory power for higher-order dimensions of psychopathology. Of course, this possibility also raises the concern that the modeling of neural influences at different levels of the hierarchy will require the use of multiple imaging paradigms in a given sample and nevertheless will be shaped by the particular selection and generality versus specificity of those paradigms.

As the authors note in their Supplement (3), the hierarchical model of psychopathology also raises thorny issues of interpretation, especially in relation to higher-level dimensions. The field is used to orthogonal conceptualizations of psychiatric disorders. Despite the inconvenient empirical cross-currents, most clinical neuroscience research continues to be done within diagnostic categories or at the level of individual symptoms, animated by the search for narrow brain-behavior mappings. The hierarchical model of psychopathology highlights what might be described as a “granularity mismatch” (9) between the brain and behavior sides of many psychopathology investigations. In other words, while it seems plausible to map out how fear circuitry might relate to phobic heart palpitations, it is a much more confounding proposition to detail how fear circuitry underpins the full range of anxious, affective, and phobic internalizing psychopathologies. Moreover, the hierarchical model does not accommodate easily to covariance strategies that are sometimes employed to “adjust for” overlapping constructs (e.g., controlling for IQ in a study focused on memory impairment in schizophrenia) (10). If variance in externalizing psychopathology is captured to a considerable extent by the general p factor, any residual of externalizing variance that remains after adjusting for the p factor may be quite different in meaning from the original construct. Indeed, Caspi *et al.* (1) reported that after the p factor was isolated as a higher-order factor, observed associations of internalizing and externalizing psychopathologies with etiological factors were uniformly reduced, often to nonsignificance. They suggested that the post-p factor internalizing and externalizing residuals might be better understood as “gendered personality styles” than as forms of “harmful dysfunction” (1).

This is not a modest proposal. Zald and Lahey (3) embrace the messy structure of psychopathology rather than defaulting to a sometimes useful but undoubtedly incomplete categorical scheme. Their proposal would require frank consideration of the ways that mental disorders overlap and new methods for studying their structure, etiology, biology, and treatment. The authors ask the clinical neuroscience field to move away from a comfortable but potentially misleading reductionism toward an integrative, far more resource-intensive, and interpretively more challenging perspective on the nature and causes of psychiatric

illness. Although the hierarchical model encompasses a daunting range of etiological possibilities for common psychiatric conditions, it is appealingly consistent with the clinical and developmental heterogeneity and the extensive comorbidities that regularly confront us in the clinic.

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