Review

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Implications of the Hierarchical Structure of Psychopathology for Psychiatric Neuroimaging

David H. Zald and Benjamin B. Lahey

ABSTRACT

Research into the neurobiological substrates of psychopathology has been impeded by heterogeneity within diagnostic categories, comorbidity among mental disorders, and the presence of symptoms that transcend diagnostic categories. Solutions to these issues increasingly focus neurobiological research on isolated or narrow groupings of symptoms or functional constructs rather than categorical diagnoses. We argue for a more integrative approach that also incorporates the broad hierarchical structure of psychopathological symptoms and their etiological mechanisms. This approach places clinical neuroscience research in the context of a hierarchy of empirically defined factors of symptoms, such as internalizing disorders, externalizing disorders, and the general factor of psychopathology. Application of this hierarchical approach has the potential to reveal neural substrates that nonspecifically contribute to multiple forms of psychopathology and their comorbidity and in doing so facilitate the study of mechanisms that are specific to single dimensions and subsets of symptoms. Neurobiological research on the hierarchy of dimensions of psychopathology is only just beginning to emerge but has the potential to radically alter our understanding of the neurobiology of abnormal behavior.

Keywords: Comorbidity, Externalizing, fMRI, Internalizing, Research Domain Criteria, Transdiagnostic

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The dramatic growth of cognitive neuroscience and neuroimaging over the last quarter century has produced substantial advances in our ability to examine the functioning of specific neurobehavioral circuits. However, our understanding of the neural substrates of psychopathology has not kept pace with these advances. The National Institute of Mental Health Research Domain Criteria (RDoC) initiative asserts that progress has been slowed by a focus on categorical mental disorder diagnoses (1,2). At the heart of RDoC's rationale is a concern about the limits of case-control designs in which cases meeting categorical diagnostic criteria for a mental disorder are contrasted with healthy control subjects. Such designs impose several limitations. First, the heterogeneity of symptoms among cases with the same diagnosis may obscure relations between brain functions and psychopathology, because not all cases possess the same characteristics (1,3). Second, the comorbidity of symptoms (or diagnoses) makes it difficult to ascribe observed relations to a specific target feature of cases (vs. frequently co-occurring nontarget features). Third, because case-control designs select extremely different groups of cases and control subjects, they create marked ascertainment biases. Fourth, and most important to our present argument, by limiting cases to only one diagnosis, case-control designs limit the range of symptoms that cases can exhibit, making it difficult to identify transdiagnostic mechanisms of psychopathology.

Three alternatives to case-control designs that vary in how they address the above issues have emerged in clinical neuroscience. The narrow symptom approach focuses on single symptoms or small groupings of closely related symptoms instead of diagnoses. In contrast, the broad dimensional approach focuses on overarching dimensions of psychopathology that cut across diagnoses. Alternatively, the functional constructs approach organizes research around functional processes rather than symptoms or diagnoses. These processes may be related to narrow subsets of symptoms, broader symptom dimensions, or some combination of both. We advocate for a hierarchical structural approach that integrates these three strategies to elucidate neural correlates at multiple levels of psychopathology's hierarchical structure.

A HIERARCHICAL STRUCTURAL MODEL OF PSYCHOPATHOLOGY

A core challenge for clinical neuroscience is determining the "mappings" between neurobehavioral markers and different levels of psychopathology. However, a review of the growing empirical literature on the structure of psychopathological symptoms provides clear guidance on what many of these mappings will look like. Increasingly, this literature indicates that neither a narrow nor a broad dimensional approach in isolation will allow for a full mapping of neurobehavioral systems and psychopathology. Rather, the data suggest that clinical neuroscience would profit from the adoption of a model of psychopathology in which the etiologic factors operate simultaneously at multiple levels that range from narrow mechanisms to broad nonspecific influences on mental health.

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The hierarchical structural approach to psychopathology places symptoms within an empirically determined hierarchy of dimensions. At least four levels can be identified (4). The lowest level reflects individual symptoms. The next level is formed by first-order dimensions (or factors) defined by highly correlated symptoms. Above this, broader second-order dimensions reflect the correlations among subsets of the first-order dimensions. Finally, recent data support the existence of a general factor of psychopathology that reflects the widespread positive correlations among essentially all symptoms of psychopathology (4–6).

Narrow Symptoms

Individual symptoms can be viewed as the lowest level of a symptom hierarchy. Arguably, the simplest strategy for dealing with concerns about the heterogeneity of symptoms within a diagnostic group is to examine the correlates of specific symptoms rather than diagnostic categories. This approach is especially attractive when there is a close conceptual correspondence between a specific symptom and a functional construct with known neural underpinnings. For instance, symptoms of motivational anhedonia can be linked to neurocircuitry involved in facilitating motivated responses (7). Within the context of RDoC, there are multiple examples of correspondence between a given narrow symptom and a proposed functional construct. However, such correspondence is by no means universal, because many symptoms and functional constructs defy a one-to-one relationship.

The primary limitation of focusing only at this narrow level is that psychological symptoms rarely occur in isolation (Figure 1A). When these nontarget symptoms differ from one subject to another, they can introduce heterogeneity as severe as that seen for a diagnostic category. This is not necessarily a problem if those nontarget symptoms cancel each other out in analysis. However, the associations between symptoms are often nonrandom, and when co-occurrence is high it becomes difficult to isolate relations between specific symptoms and neurobehavioral circuits or constructs. These co-occurring symptoms are often handled more reliably when aggregated into a first-order dimension.

First-Order Dimensions of Psychopathology

Frequently co-occurring symptoms are often handled by aggregation into first-order dimensions. Factor analysis studies indicate that these first-order dimensions generally (but not universally) parallel different DSM-IV/DSM-5 diagnoses (8–13), although there is some circularity in such studies given that the symptoms queried are frequently limited to those that are included in the DSM. Examination of first-order dimensions instead of diagnoses may nonetheless aid in neuroimaging research to the extent that they better capture the dimensional nature of psychopathology and eliminate artificial boundaries between diagnostic groups and clinical versus subclinical diagnostic distinctions (14).

Correlations Among First-Order Dimensions and Comorbidity

Although studying first-order dimensions provides an empirical refinement over categorical diagnoses, as seen in Figure 1B, these dimensions (and the parallel categorical diagnoses) are far more correlated than orthogonal (15–21). This comorbidity has often been treated as a failure of the current diagnostic system to achieve the Platonic ideal of "carving nature at its joints." We believe that clinical neuroscience research needs a paradigm shift in conceptualizing the high correlations among dimensions or disorders. Correlations among first-order dimensions of psychopathology should not be viewed as flaws, but rather as important sources of information about the nature and etiology of psychopathology (15,18,22,23). This shift has already begun to take hold in behavior genetics (23–26). It is arguably time for clinical neuroscience to take similar notice.

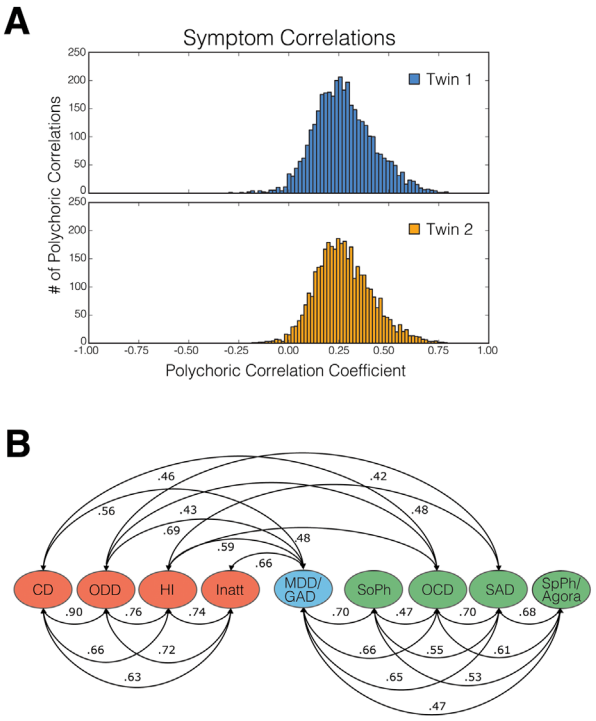

Figure 1. **(A)** Histograms of polychoric correlations among psychopathology symptoms based on caretaker interview with the Child and Adolescent Psychopathology Scale (73) for adolescents in wave 1 of the Tennessee Twin Study (16). Although there is variability in the magnitudes of correlations, most symptoms show at least modest positive correlations with a broad array of other symptoms. Note: A small number of items with correlations ± 4 standard deviations below the mean were excluded. In each case, these involved items with extremely low endorsement rates. **(B)** Correlations among first-order latent dimensions of psychopathology in wave 1 of the Tennessee Twin Study based on the same symptoms. Note: Only correlations greater than $r = .40$ are shown, but all additional correlations are statistically significant. Agora, agoraphobia; CD, conduct disorder; GAD, generalized anxiety disorder; HI, hyperactivity-impulsivity; INATT, inattention; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; SAD, separation anxiety disorder; SoPh, social phobia; SpPh, specific phobia. [Figure 1B adapted with permission from Lahey *et al.* (16) Figure 5.]

Second-Order Dimensions and the General Factor of Psychopathology

Factor analysis of the covariance of first-order symptom dimensions generate second-order factors. Two second-order