Transdiagnostic factors of mental disorders

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Official nosological systems, such as the DSM-5 and ICD-10, define psychopathology and substance use disorders as distinct, independent, and categorical constructs. In other words, the classification systems imply that a patient either meets the diagnostic threshold for a particular mental disorder or does not (categorical), the disorder does not overlap with other disorders (distinct), and therefore presence of the disorder should not necessarily be associated with a higher probability of having another disorder (independent).

Both clinical experience and empirical research indicate that these assumptions are not justified, however. First, subthreshold disorder manifestations can be associated with significant distress and dysfunction; moreover, there are important severity differences among individuals receiving the same diagnosis. This suggests an underlying dimensionality to mental disorders not captured by categorical diagnoses and highlights the information lost when reducing a complex constellation of signs and symptoms to a present-absent dichotomy. Second, comorbidity is the rule, rather than the exception. Individuals who have one disorder are likely to meet criteria for additional disorders at rates far exceeding what would be predicted from disorder prevalence rates.

Research on disorder dimensionality and comorbidity suggests that many mental disorders are manifestations of relatively few core underlying dimensions. Beginning several decades ago, investigations of common symptoms and behaviors in children, and diagnoses in adults, have repeatedly replicated such an underlying cross-cutting transdiagnostic structure: the internalizing-externalizing model. *Internalizing* accounts for comorbidity among major depression, generalized anxiety disorder, dysthymia, panic disorder, social and specific phobias, post-traumatic stress disorder, and so on, while *externalizing* accounts for comorbidity among substance use disorders and antisociality-, behavioral-, and impulsivity-related disorders.

Unlike the organizations of many official nosologies (e.g., "mood disorders" as separate from "anxiety disorders"), this internalizing-externalizing model provides excellent fit to the data and has been replicated in various populations, from around the world (1,2). This report highlights recent advances and contemporary directions in transdiagnostic comorbidity research.

THE NATURE OF INTERNALIZING AND EXTERNALIZING

Disorder persistence

Studies have shown that internalizing and externalizing are quite stable over time, which has marked implications for understanding successful psychological aging as well as disorder persistence. Indeed, research on this question illustrates that these two transdiagnostic factors are key to understanding disorder continuity. The transdiagnostic variance that related disorders share (captured by the factors) appears to drive disorder persistence. On the other hand, the unique variance of disorders – disorder-specific variance that makes each disorder different from its related disorders – tends to show comparatively low, often negligible, stability. In other words, internalizing and externalizing appear to serve as the primary pathway for homotypic disorder persistence over time. Generalized anxiety disorder, for instance, appears to persist because the internalizing factor variance saturates the diagnosis, and it is this transdiagnostic variance that is stable, not the disorder-specific variance (3,4).

Disorder onset

Since the factors account for the majority of homotypic continuity over time, investigations of their role in heterotypic continuity and disorder onset are crucial. For instance, one can conceptualize lifetime transdiagnostic factor levels as a liability for subsequent disorder onset and thus as the key drivers of the development of sequential comorbidity. In longitudinal onset data on eighteen disorders, Kessler et al (4) applied a novel time-lagged latent comorbidity survival model, and found that internalizing and externalizing at time 1 accounted well for subsequent onset of new disorders. This highlights the need for latent structure modeling to move beyond cross-sectional data into well-characterized longitudinal datasets.

Factor characteristics

Researchers have recently addressed three important questions about transdiagnostic factors' characteristics. First, how is the distribution of these factors best conceptualized? This distributional question is important in that it allows for a better understanding of latent internalizing and externalizing generally, and it thus helps us understand the dispersion of these factors in the population. Multiple studies now indicate that these factors are continuously distributed dimensions (vs. liability classes, or dimension-class hybrids) (3).

Second, how similar (invariant) are these factors across different groups? Studies of internalizing-externalizing across several populations – comparing individuals by gender, race/ethnicity, age, and sexual orientation – have repeatedly

replicated the finding that internalizing and externalizing are invariant (3,5,6). This indicates that the reason mental health disparities are observed in particular disorders is because groups differ in their average transdiagnostic factor levels. Women thus report higher rates of major depression than men because women, on average, have higher levels of internalizing than men.

Third, are these factors best thought of as single factors or as subsuming sub-factors? The answer to this question points to a hierarchical account. Investigations of externalizing typically suggest a single factor in adulthood; however, correlated sub-factors (e.g., substance use) can also emerge. Regarding the higher-order structure of internalizing, some studies support a single internalizing factor and others find that internalizing subsumes two lower-order factors: *distress* (major depression, generalized anxiety, dysthymia) and *fear* (agoraphobia, social phobia, specific phobia).

DISORDER RELATIONS WITH OUTCOME AND EXPOSURE

Internalizing and externalizing, unlike disorder-specific variance, predict subsequent disorders, but what role do they play in linking disorders with other important variables? A growing number of studies indicate that disorders' associations with important outcomes are driven by transdiagnostic variance rather than disorder-specific variance. For instance, the association between major depression and suicidal behavior largely seems to reflect depression's association with internalizing, not something particular about depression (3).

In terms of the links between environmental exposures and disorders, studies suggest that transdiagnostic factors largely mediate these associations, meaning that an exposure (e.g., discrimination, adverse childhood experiences) likely raises transdiagnostic factor levels, which manifest as higher rates of multiple observed disorders (5). These findings clarify the diffuse impact of individual exposures on multiple disorders.

Given that transdiagnostic factors appear to account for the majority of the associations between exposures and disorders, disorders and subsequent disorders, and disorders and outcomes, a significant future research question involves determining what, if anything, disorder-specific variance tells us above and beyond transdiagnostic factors.

TOWARD A COMPREHENSIVE TRANSDIAGNOSTIC MODEL

Bifactor models

One recent development has been the application of new transdiagnostic models. Internalizing and externalizing are correlated, suggesting the presence of another factor to account for this association. Bifactor models, positing a general psychopathology factor that saturates all diagnoses (in addition to internalizing and externalizing), are gaining empirical traction (7,8). Bifactor models will be a key future direction for understanding comorbidity at the most general level.

New disorders and factors

Transdiagnostic factor models typically are modeled to characterize comorbidity of common mental disorders. However, such models can also capture other disorders, such as schizophrenia spectrum, eating, and sexual functioning disorders. While some of these less common disorders reflect internalizing and externalizing, others represent additional factors. For instance, schizophrenia and related psychotic disorders reflect a unique thought disorder factor (9), and autism spectrum disorders reflect a unique factor as well (10). Expanding transdiagnostic comorbidity models to include new disorders and new factors is a prime future direction.

Links with personality

Internalizing and externalizing are associated with personality traits, such as negative affect and disinhibition, respectively. In terms of abnormal personality, many categorical personality disorders also can be fit into this model. The recent DSM-5 reconceptualization of personality disorders via an alternative dimensional system (11) provides a fertile new research avenue. Indeed, DSM-IV personality disorders can be understood as manifestations of specific combinations of specific facets of these broader dimensions. These domains' link to mental disorder conceptualized more broadly is also clear: at a higher-order level, these domains converge into internalizing and externalizing (12).

INTERVENTION IMPLICATIONS

Transdiagnostic factor models inform intervention in two major ways. The first is conceptual: they help explain why certain psychopharmacological agents, and particular psychotherapy modalities, are effective for multiple, allegedly distinct conditions. Second, they provide a target of intervention: if treatments can lower transdiagnostic liability levels, they may have general impacts across multiple disorders and thus prove efficient. Indeed, one such transdiagnostic treatment is available for emotional (internalizing) disorders, and this is a key direction for intervention research (13).

TRANSDIAGNOSTIC FACTORS IN THE RDoC ERA

Research funding is increasingly focusing on biological investigation of mental disorder, epitomized by U.S. National

Institute of Mental Health's Research Domain Criteria (RDoC) (14).

Transdiagnostic factors are poised to play a major part in RDoC-oriented investigations of psychopathology. First, these factors represent primarily genetic variance (15), highlighting their potential utility in genetic investigations. Second, these factors are closely associated with neurobiological systems, such as internalizing's association with the emotional circuitry common to emotional disorders (13,16).

As such, transdiagnostic factors appear uniquely suited to bridge psychiatric phenomena and biological substrates of behavior, and they thus appear crucial considerations in the RDoC era as research moves increasingly away from categorical diagnoses derived from patient interviews (5,7).

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