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EDITORIAL

Latent variable and network models of comorbidity: toward an empirically derived nosology

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Although current classification systems, such as the diagnostic and statistical manual of mental disorders (DSM-5) [1], define mental disorders as putatively independent phenomena, comorbidity is the rule rather than the exception. Indeed, nearly half of individuals meeting criteria for one mental disorder will meet criteria for at least one more [2]. Through bivariate analyses, we can note that disorders such as major depressive disorder (MDD) and generalized anxiety disorder (GAD) overlap more frequently than expected by chance alone [3–5]. Based on their prevalence rates, data from one nationally representative sample indicated four individuals per 1,000 should have comorbid MDD and GAD; however, 17 such cases—more than 400 % of the expected frequency—were observed [5].

High rates and diffuse patterns of comorbidity suggest fundamental problems with current nosologies. To many, they also represent foci for classification research in that understanding the nature of comorbidity may help characterize the fundamental, transdiagnostic building blocks of psychopathology and thereby reconceptualize psychiatric constructs. Thus, framing comorbidity as a meaningful subject of inquiry in itself, rather than as a failure of classification systems that should be remedied, presents an exciting opportunity to understand what mental disorder really is. Ideally, by bootstrapping from imperfect nosologies, we can iteratively improve the validity of our diagnostic constructs and eventually produce a close fit between the model (nosology) and the data (observed manifestation of psychopathology in individuals).

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Latent variable models of comorbidity

For the past few decades, researchers have applied a variety of latent variable models to characterize comorbidity among signs and symptoms of given disorders as well as among diagnostic entities themselves. These models are based in the same factor analytic tradition that yielded the *g* factor of intelligence [6] and big five personality domains [7–9]. Put simply, these models posit that the observed associations among measured variables can be thought of as consequences of one or more latent (unobserved) variables [10]. These latent variables form the basis of the common factor model: Various tests that tap into different types of intelligence relate positively to one another because they are all saturated by a latent *g* factor, and personality questionnaire items about interest in talking to people, going to parties, and so on relate positively to one another because they are all saturated by a latent extraversion factor.

When applied to diagnostic data, latent variable modeling approaches suggest latent factors that account for observed multivariate comorbidity among disorders. Early applications of this approach to psychopathology data indicated that children's symptoms and behaviors tended to covary broadly in two fundamental ways, suggestive the presence of two latent variables: internalizing and externalizing [11, 12]. Subsequent application in adult psychopathology data [13, 14] led to a proliferation of latent variable modeling studies replicating this structure [15–22], where the internalizing latent variable represents comorbidity among unipolar mood and anxiety disorders, and externalizing represents comorbidity among substance use disorders and various impulsivity-, oppositionality-, and antisociality-related disorders.

Latent variable modeling of these comorbidity factors has proven quite scientifically generative. These latent

variables have been shown to be largely genetic in origin [23], but they also can be impacted by environmental exposures, such as childhood maltreatment and victimization and harassment experiences [24, 25]. They appear across numerous nationalities and cultures [22], and they are invariant across age [26], gender [16, 21, 27], race/ethnicity [20], and sexual orientation [25]. They account for the development of lifetime comorbidity and continuity of disorders over time [18, 26, 28]. They relate closely to personality traits [29], and they account for the links between disorders and important outcomes, such as suicide [28, 30]. They are also a growing focus of potentially effective and efficient interventions—by treating the underlying core of multiple disorders, it is hoped that intervention could have a diffuse effect [31, 32].

Network models of comorbidity

In the past several years, a different conceptualization of comorbidity—the network model—has been presented [33–35]. A compelling new direction, network model proponents largely reject the latent variable explanations of comorbidity in favor of the notion that mental disorders are composed of networks of causally connected symptoms. Some of these symptoms cause symptoms in other disorders' networks, and, together, can characterize a broad network of associations among disorders and thus comorbidity. This network approach accounts for comorbidity without many of the assumptions of the latent variable model, including the presence of higher-level latent comorbidity factors that cause observed comorbidity. For instance, network models do not assume that a disorder is measured or indicated by its symptoms, which is a foundation of the latent variable model; rather, the network approach says that the symptoms themselves are "connected through a dense set of strong causal relations" [33]. By not assuming that a latent disorder variable causes all manifested symptoms of a disorder, dynamic flexibility is introduced. For instance, while a latent variable model would indicate that MDD symptoms of sleep disturbances and fatigue were both largely caused by the latent depression variable, the network model could account more easily for the possibility that the sleep disturbances directly caused the fatigue, and that this causal observation does not require an unobserved variable to account for it [33].

Application of network models suggests that half of the symptoms of DSM-IV are connected in a network fashion [35], providing an alternate view of comorbidity—wherein particular symptoms cause one another dynamically, and where disorders are linked by symptoms that bridge their networks—that does not require broad latent variables. Rather than MDD and GADs observed comorbidity representing manifestations of a latent internalizing variable, proponents of network models argue that this comorbidity is thus due to direct causal links among symptoms. A result is a visual depiction of the symptom network, which illustrates the pattern and strength of associations among symptoms as well as the centrality of a particular symptom to a given network.

This network model of comorbidity turns analysis of comorbidity on its head, eliciting both supportive and critical feedback from scholars. While some researchers resonate with the novelty and promise of network models [36–38], others claim that network model proponents compare their models to strawman latent variable models [39] and suggest we know more than we do about observed phenomena [40]. Because network comorbidity models can include a great number of parameters, they have been criticized for their lack of parsimony and thus perceived as unlikely to uncover basic organizational structures that can become the focus of scientific inquiry [41]. This allegation stands in contrast to latent variable models, which reduce dimensionality of a space and thus produce investigable constructs such as internalizing, which, for instance, has subsequently been shown to be nearly perfectly correlated with trait neuroticism [29].

Toward an empirically derived nosology

The latent variable and network model conceptualizations of comorbidity have been framed as something of a competition, wherein researchers in one camp challenge the methodology of the other. In my view, it is obvious that both models have strengths and limitations. Thus, the question is not whether we should use latent variable or network models; the question is how best to use both to inform nosology. Both approaches represent potentially potent tools in the psychopathologist's toolkit, and, as has been noted, latent variable models can be thought of as a class of network models [42]. Even in light of their limitations, latent variable models have proven to be highly generative in advancing theory and, with the organizational meta-structure of DSM-5 reflecting these latent variables and treatments being developed to target them, they influence classification, assessment, and practice as well. While there are concerns that network models, due to their general lack of parsimony and comparatively more difficult interpretation, may not be as generative [41], the potential of this new class of models to inform research likely remains to be fully realized. From Achenbach's pioneering work [11, 12] with children, it took decades for the latent variable model of comorbidity to take hold firmly, and only time will tell if network models are as informative in classification research as they have been for other diverse

topics, like neural systems, power grids, and World Wide Web structure [33].

In this era of NIH's Research Domain Criteria, issues of classification and construct refinement are increasingly coming to the fore as researchers attempt to link psychiatric phenotypes with biological substrates. Latent variable and network modeling approaches represent key players in this endeavor, particularly insofar as they can highlight core psychiatric phenomena that account for observed symptomatological and diagnostic comorbidity or identify central, highly connected nodes, respectively. Reliable and valid phenotypes can serve as targets for molecular genetic and functional imaging analyses, among others, and both modeling approaches to comorbidity appear potentially highly informative for classification (Johnson).

If the goal is to determine the core constructs of psychiatry and develop an empirically derived nosology, the more modeling options researchers have at their disposal, the better. These are thus exciting times in classification research, for several reasons. First, the proliferation of multiple new types of latent variable models—for instance, those incorporating latent class and latent trait structures simultaneously [28, 43]—allow new options for testing latent structure, particularly given the possible taxonic distributions of some disorders [44]. These variable-centered analyses, coupled with person-centered approaches such as model-based cluster analysis, hold great potential.

Second, a focus on causality, including using time-sensitive longitudinal modeling approaches, may be highly informative [45]. While neither latent variable or network models can demonstrate causality directly [46], thoughtful use of both models can highlight areas likely causal pathways. An increased focus on well-characterized longitudinal psychopathology data will also help adjudicate possible causal links, as can be seen by recent time-sensitive survival-type analysis of person-years in the development of lifetime comorbidity [18, 47]. Incorporating approximated counterfactuals, through structural equation [48–50] and novel co-twin control analyses [51–53], within these comorbidity models will also likely prove beneficial in understanding causality.

Finally, construct refinement does not need to focus solely on the level of diagnoses. Rather, symptom-level analyses in latent variable and network approaches [33, 43, 54] can be highly informative. Indeed, this appears to be an area in which the measurement focus of latent variable models might be highly compatible with the network approach, wherein imperfectly measured symptoms could be treated as latent variables with multiple indicators [55]. The pathways among, and relative importance of, these latent symptom variables could be assessed through a network modeling approach.

Summary

Latent variable models of comorbidity have significantly advanced the field of psychopathology and have proven highly generative in both research and applied contexts. Network models are relatively new in comorbidity research, and they have yet to receive a similar degree of application. While frequently framed as competing models, there is no reason to believe any single model will definitively capture comorbidity patterns and refine psychiatric nosology. In tandem with other analytic advances, however, these approaches can likely highlight key constructs at the observable and latent levels, which can be used to bootstrap from imperfect nosologies to more valid ones, iteratively. All models have strengths and weaknesses. Building upon a common quotation [56], all psychopathology models are wrong, and certainly incomplete, but some of them are useful. Thus, rather than asking which tool is best for all purposes, comorbidity and classification researchers should ask which tool is most appropriate for a given purpose—and how these sophisticated tools can complement one another to capture phenomena as complex as mental disorder.

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