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The role of latent internalizing and externalizing predispositions in accounting for the development of comorbidity among common mental disorders

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Abstract

Purpose of the review—Although numerous studies have examined the latent *structure* of internalizing and externalizing mental disorders, the effects of this structure in predicting the *development* of comorbidity have remained unexamined until recently.

Recent findings—A novel approach to study the effects of latent internalizing and externalizing predispositions to the development of comorbidity was used to analyze data from 14 countries in the WHO World Mental Health (WMH) Survey Initiative. Pervasive significant positive associations were found between temporally primary and secondary internalizing and externalizing disorders in survival analyses, with time-lagged associations consistently stronger within-domains than between-domains. The vast majority of these associations were explained by latent internalizing and externalizing variables. Specific phobia and OCD were the most important internalizing components and hyperactivity disorder and oppositional-defiant disorder the most important externalizing components. Several intriguing residual time-lagged associations remained significant, though, even after controlling latent predispositions.

Summary—The latent variable model suggests that common causal pathways account for most comorbidity among internalizing-externalizing disorders. These pathways should be the focus of future research on the development of comorbidity, although isolation of consistent residual time-lagged associations between certain pairs of primary-secondary disorders is also important in pointing the way to subsequent focused study.

Keywords

Comorbidity; Epidemiology; Risk factors

INTRODUCTION

Comorbidity is the norm among common mental disorders, as more than 50% of people with a mental disorder in a given year have multiple disorders [1, 2]. The structure of this

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comorbidity has been the subject of considerable interest over the past decade. Beginning with an influential paper by Krueger [3], numerous researchers have used factor analysis to document that associations among hierarchy-free anxiety, mood, behavior, and substance disorders can be accounted for by correlated latent predispositions to internalizing (anxiety, mood) and externalizing (disruptive behavior, substance) disorders. The internalizing dimension is sometimes further divided into secondary dimensions of fear (e.g., panic, phobia) and distress (e.g., major depressive episode, generalized anxiety disorder) [4-9]. These results have been used to argue for a reorganization of the classification of mental disorders in the DSM and ICD diagnostic systems [10-14], although other data suggest that this theoretical structure might be insufficiently robust to serve as the basis for such a reorganization [4, 15]. For example, the distinction between fear and distress disorders does not emerge in all studies [4, 15-17] and model fit deteriorates when additional disorders are added or when the model is estimated separately among people at different life-course stages [13, 15].

Despite these inconsistencies, the general finding of strong comorbidity within the internalizing and externalizing domains has raised the question whether common risk factors exist for the disorders in either of these domains and, if so, whether risk factors for individual disorders documented in previous studies are actually risk factors for these broader predispositions. The issue of specificity vs. generality of risk factors is of considerable importance, as a number of hypotheses about causal pathways posit the existence of very specific associations between particular risk factors and particular outcomes. These interpretations would be called into question if empirical research showed that the risk factors had less specific predictive effects [18]. In addition, evidence that a risk factor had a broad effect on a wide range of disorders would increase interest in that risk factor as an intervention target [19].

Although the use of latent variable models to study risk factor specificity is only in its infancy, research already has shown that this line of analysis has considerable value in distinguishing specific versus nonspecific risk factors. For example, Kramer and colleagues [20] found that the widely-observed association of gender with depression became insignificant when controls were included for latent internalizing and externalizing dimensions, arguing that gender is more directly associated with these overall latent dimensions than with depression or any other disorder within these dimensions. In another example, Kessler and colleagues [21] found that the effects of childhood adversities on onset of individual mental disorders were largely mediated by more direct effects on predispositions for internalizing and externalizing disorders.

One special class of latent variable risk factor studies uses samples of twins to estimate the effects of genetic factors on comorbidity. These studies have shown that much of the comorbidity between particular pairs of mental disorders in epidemiological samples, such as between eating disorders and substance use disorders [22] or nicotine dependence and major depression [23], can be explained by a latent variable model that assumes the existence of genetic influences. More elaborate studies of a related sort have shown that much of the comorbidity among anxiety disorders [24] and among personality disorders [25] can be explained by models that assume the existence of genetic influences. Other studies have shown that the inter-generational continuity of childhood-onset externalizing disorders can be explained by a model that assumes the existence of genetic transmission [26] and that decomposition of factor analyses into separate additive genetic and environmental components finds stable internalizing and externalizing factors only for genetic, not environmental, influences [27**, 28].

It is important to note that the findings of strong genetic influences on comorbidity are constrained by the additivity (i.e., no interactions between genetic and environmental effects) and equal environment (i.e., comparability of environmental similarity between identical and non-identical twins) assumptions that are needed to identify the coefficients in standard behavior genetic models. These assumptions have long been the subject of controversy, especially the additivity assumption [29]. Great care is consequently needed in interpreting these results because of their sensitivity to these assumptions [30**]. An additional important implication, even if we are prepared to accept the results of variance-covariance decomposition analyses based on twin studies, is that the term “genetic” has a much broader meaning than typically appreciated. For example, as noted famously by Lewontin many years ago [29], a genetic effect on tryptophane metabolism that has mediating effects through “melanin deposition to skin color to hiring discrimination to lower income” would emerge in a standard twin analysis as documenting strong “heritability for ‘economic success’” even if the true driving force behind the association was hiring discrimination based on skin color.

The risk factor studies described above treated latent measures of internalizing and externalizing predispositions as independent variables in causal models that predict individual disorders. Most of these studies use cross-sectional data and assess comorbidity at a point in time. Although several other studies have used longitudinal data to determine whether the structure of internalizing and externalizing disorders is stable over time [9, 15, 16], none tried to predict onset or persistence of disorders prospectively. Other longitudinal studies examined temporal progression [31-34] or sequencing [35-39] between earlier and later disorders, documenting strong persistence of disorders over time and predictive associations between some but not other temporally primary and later disorders. Again, though, none of these studies investigated the extent to which associations of earlier disorders with later disorders were explained by latent internalizing or externalizing variables. For example, Fergusson and colleagues [31] found that childhood conduct disorder but not ADHD predicted subsequent onset of substance disorders, while Beesdo et al. found that temporally primary social anxiety disorder predicted subsequent onset and persistence of major depression [40], but did not study whether these associations were due to effects of latent internalizing or externalizing predispositions.

Previous reviews of the developmental psychopathology literature suggest that analysis of the effects of latent predispositions to mental disorders on onset and progression of individual disorders could be very useful in identifying modifiable risk pathways [41, 42]. The confirmatory factor analysis approach that has dominated the literature on latent variables in comorbidity does not allow this kind of investigation. However, a new approach to the analysis of comorbidity makes this possible. This new approach is explicated here and illustrated with an analysis of predictive effects between latent predispositions to internalizing and externalizing disorders and subsequent first onset of Axis I disorders in the WHO World Mental Health (WMH) Surveys [43**].

THE APPROACH

Factor analytic studies of comorbidity decompose correlation matrices among point-in-time disorders to study the structure of cross-sectional associations. However, point-in-time prevalence is a joint function of lifetime risk and persistence. Factor analysis cannot break prevalence estimates into these two components. When data are available on age-of-onset (AOO) and persistence of multiple disorders, though, this decomposition can be made by using survival analysis [44] to carry out separate studies of (i) the associations of prior lifetime disorders with subsequent first onset of some other disorder and (ii) the associations

of lifetime comorbidity with persistence of that other disorder. Backwards recurrence models can also sometimes be used to study predictors of persistence [45].

Consider a situation where we are studying comorbidities among D disorders with a focus on predictors of first lifetime onset. We would have D survival equations (i.e., one to predict onset of each disorder). There would be $D-1$ predictors in each equation (i.e., one predictor for prior lifetime occurrence of each other disorder at time t to predict onset of a focal disorder between times t and $t+1$) and $D \times (D-1)$ coefficients across all the equations. (Figure 1) The latent variable formulation we propose, in comparison, assumes that these coefficients are mediated by latent predispositions to internalizing and externalizing disorders that can change between times t and $t+1$. (Figure 2) As these two models are nested (i.e., the model in Figure 2 is a special case of the model in Figure 1), it is possible to compare model fit using standard fit indices. It is also possible to modify the model to allow for direct effects of some temporally primary disorders on subsequent onset of some secondary disorders. The model can also be elaborated to consider more than two latent variables.

This latent variable model cannot be estimated with the covariance structure analysis approach used in previous studies of the structure of comorbidity, as the number of person-years in the survival analysis varies across outcomes. It is also important to note that model does not assume a factor analytic structure in which the latent variables *cause* the observed disorders and the prediction errors for the observed disorders are conditionally independent. Instead, we assume that the observed disorders are the *predictors* of the latent variables. These predictors can be inter-correlated at time t because of joint influences. In this way, the model assumes that the latent variables represent common pathways by which the time t predictors influence multiple outcomes at time $t+1$.

Estimation of model coefficients is complicated by the fact that we are dealing with survival models across a range of outcomes in which first onsets vary from person to person and from year to year. Iterative methods are consequently needed to estimate model coefficients. We did this using a discrete-time (i.e., person-year) framework where each value of t represents one year of the respondent's life. We consider each of three main parts of the model separately (time t observed variables predicting time t latent variables, time t latent variables predicting time $t+1$ latent variables, time $t+1$ latent variables predicting time $t+1$ observed variables), estimate coefficients only in one of these three parts at a time while fixing coefficients in the other two parts to their values in the most recent iteration, and then repeat this process sequentially until estimates converge. This yields maximum-likelihood estimates of model parameters. A likelihood-ratio χ^2 test can be used to compare model fit with the observed variable model.

This model can also be estimated at separate points in the life course. And it can determine if particular pair-wise associations between observed time t lifetime disorders and onset of outcome disorders at time $t+1$ are significant after controlling the latent variables. The latter can be done by using empirical estimates of time t latent variables (generated from model coefficients) as controls in separate bivariate survival equations that predict first onset of each disorder from prior history of each of the other disorders. And, of course, this entire system of associations can be included in more complex models that examine other predictor associations (e.g., the association of gender with first onset of major depression) to determine if the latent variables account for those associations.

IMPLEMENTATION IN THE WORLD MENTAL HEALTH SURVEYS

As reported in more detail elsewhere [43**], this approach was used to study the structure of lifetime comorbidity among the 18 DSM-IV disorders assessed in the WHO World Mental

Health (WMH) surveys, a series of community epidemiological surveys administered to 21,229 respondents across 14 different countries [46]. Preliminary analysis found that point-in-time comorbidity among these disorders fit a two-factor internalizing-externalizing disorders factor model. Retrospective AOO reports were then used to estimate a series of 18 survival equations in which first onset of each core disorder was predicted by prior lifetime onset of the other 17 disorders along with basic socio-demographic controls. 98.0% of the 306 (18x17) survival coefficients were positive and 95.1% significant in bivariate analysis. 80.0% of survival coefficients were positive and 43.0% positive and statistically significant in multivariate analyses. Within-domain time-lagged associations were generally stronger than between-domain associations.

The latent variable model was then estimated and was found to fit the data much better than the observed variable model. The most important predictors of the latent variables were specific phobia and obsessive-compulsive disorder for the internalizing dimension and hyperactivity disorder and oppositional-defiant disorder for the externalizing dimension. Controls for the latent variables explained the vast majority of the originally significant time-lagged associations among observed disorders. Most of the 13 residual pair-wise time-lagged associations between observed disorders that remained significant involved either (i) within-disorder reciprocal associations (e.g., attention-deficit with hyperactivity disorders; overt and covert subtypes of conduct disorder), (ii) asymmetrical associations between well-known disorder pairs (panic predicting agoraphobia and major depression predicting GAD), and (iii) likely diagnostic confusions (agoraphobia predicting specific phobia and hyperactivity disorder, but not attention-deficit disorder, predicting bipolar disorder).

IMPLICATIONS

The good fit of the latent variable model suggests that common causal pathways account for most comorbidity among the disorders considered. A similar pattern was found in preliminary analysis of several other datasets [47]. Ongoing analyses of these data are exploring more refined specifications that examine variation in the relative importance of different temporally primary disorders in predicting subsequent onset of secondary disorders at different points in the life course. These analyses are also investigating the possibility of synergistic effects of comorbid primary disorders. The latent variable modeling approach used here is very flexible in allowing these types of elaborations to be considered.

Based on the results of the WMH analyses as well as the confirmatory results of the additional analyses described in the previous paragraph, it appears that the common pathways defined by latent internalizing and externalizing variables (and possible expansion of these latent variables to include more refined distinctions among disorders) should be the focus of future research on the development of comorbidity. The analyses carried out so far show that more differentiation across disorders can be found in the *predictive* associations of temporally primary disorders with subsequent onset of secondary comorbid disorders than in the *point-in-time* associations between prevalent disorders. This makes it possible for us to pinpoint critical seed disorders that are associated with high risk of subsequent onset of *lifetime* comorbidity. Parallel analyses are needed to determine which primary disorders (or constellations of comorbid disorders) predict disorder persistence so as to increase our understanding of the dynamic influences on *episode* comorbidity.

It is also important, though, to recognize the existence of several important residual associations that cannot be explained by the mediating role of latent predispositions. We noted in the introduction that latent variable models can be useful in helping to determine when associations thought to be specific (e.g., a positive association between female gender and depression) are really part of a more general pattern (e.g., a positive association between

female gender and internalizing disorders, with no special elevation of the association with depression compared to other internalizing disorders). The flip side of that issue is that latent variable models provide a unique way to search through a large number of associations to distinguish the few that are specific from the larger number that are general. Consistent evidence across studies of the existence of particular specific associations can be valuable in calling attention to the importance of these associations as a preliminary to carrying out more focused studies of these associations.

SUMMARY

- Although numerous factor analysis studies of point-in-time comorbidity among mental disorders document the existence of latent predispositions to internalizing and externalizing disorders, it has only been recently that research has begun to study the effects of latent predispositions in predicting the *development* of comorbidity.
- A novel survival analysis with mediating latent variables applied to 14 epidemiological surveys collected in the WHO World Mental Health Survey Initiative showed that the consistently significant positive associations found in observed-variable models between most temporally primary lifetime disorders and subsequent first onset of most secondary disorders could largely be explained by the mediating effects of latent internalizing and externalizing variables, although, a number of intriguing residual time-lagged associations remained even after controlling these latent predispositions.
- The good fit of the latent variable model suggests that the common causal pathways that account for most comorbidity among internalizing and externalizing disorders should be the focus of future research on the development of comorbidity, although the analysis approach described here provides a unique way to pinpoint significant residual associations that should also be the subject of further focused study.

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Figure 1. Schematic of the multivariate observed variable model¹

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¹Only three observed lifetime time t internalizing disorders (e.g., i_{1t} represents internalizing disorder 1 at time t) and externalizing disorders along with only one observed internalizing and one observed externalizing disorder at time $t+1$ are shown to simplify the presentation. First onset of each of these disorders between times t and $t+1$ was predicted by prior lifetime history of the other disorders as of time t . Estimation was made in D separate survival equations, each with $D-1$ predictors for prior history of the other disorders, for a total of $D \times (D-1)$ pair-wise time-lagged associations between earlier and later disorders. The $D-1$ predictor disorders are treated as time-varying covariates in a discrete-time (person-year) survival framework.

Figure 2. Schematic of the multivariate latent variable model¹

A version of this figure was originally published in Kessler, R.C., Ormel, J., Petukhova, M., et al. (2011). Development of lifetime comorbidity in the World Health Organization World Mental Health Surveys. *Archives of General Psychiatry* 68(1), 90-100, © 2011 American Medical Association. Used with permission.

¹Only three observed lifetime time t internalizing disorders (e.g., i_{1t} represents internalizing disorder 1 at time t) and externalizing disorders and only three disorders of each set at time $t+1$ are shown to simplify the presentation. These latent variables, in turn, were predicted by lifetime history of latent internalizing and externalizing variables as of time t . These time t latent variables, finally, were predicted by lifetime history of observed internalizing or externalizing variables as of time t . Estimation was carried out using a three-part iterative procedure. See the text for more details. As in the earlier observed variable model, the predictor disorders were treated as time-varying covariates in a discrete-time (person-year) survival framework.