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Reinterpreting Comorbidity: A Model-Based Approach to Understanding and Classifying Psychopathology

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Abstract

Comorbidity has presented a persistent puzzle for psychopathology research. We review recent literature indicating that the puzzle of comorbidity is being solved by research fitting explicit quantitative models to data on comorbidity. We present a meta-analysis of a liability spectrum model of comorbidity, in which specific mental disorders are understood as manifestations of latent liability factors that explain comorbidity by virtue of their impact on multiple disorders. Nosological, structural, etiological, and psychological aspects of this liability spectrum approach to understanding comorbidity are discussed.

Keywords

DSM; statistics; multimorbidity; personality; genetics

INTRODUCTION

The comorbidity phenomenon poses a significant conceptual problem in both clinical and research work with psychopathology. In the clinic, how shall we conceptualize cases that seem to exemplify putatively distinct forms of psychopathology simultaneously? In research, how do we choose cases to study when the typical case does not fit neatly into a specific diagnostic category?

The prevalence and extent of the comorbidity phenomenon has led to a very large literature documenting comorbidity across the range of psychopathology characterized in current nosologies. Previous contributions to the *Annual Review of Psychology* (Clark et al. 1995, Mineka et al. 1998, Widiger & Sankis 2000) have emphasized this point and can be consulted for evidence that comorbidity is a highly general phenomenon; no diagnostic grouping appears to be entirely “safe” from extensive comorbidity. The current chapter therefore has a somewhat distinct purpose. Our goal is not to further document the comorbidity phenomenon per se, the prevalence and importance of which seems clear from the existing literature. Rather, the goal of this chapter is to reinterpret comorbidity by focusing on literature providing novel approaches to understanding and classifying psychopathology. These novel approaches have the potential to resolve many of the conceptual problems inherent in the comorbidity phenomenon.

The rarity of cases that are well described as meeting criteria for a single form of psychopathology signals to us the need for fundamental changes in the way we think about classifying psychopathology. Historically, psychopathology has been thought of in terms of putatively distinct categories, where membership in a category is a matter of having a sufficient number of symptoms. Various combinations of symptoms are regarded as sufficient to qualify a person as a member of a category, so long as the correct numbers of symptoms are present. This approach is frequently termed a “categorical-polythetic” approach, in the sense that

psychopathology is thought of in terms of a number of categories, and there are multiple ways of meeting criteria for category membership (membership in a class is polythetic). Nevertheless, this is only one potential way to conceptualize psychopathology, and it may not be the most optimal approach. Other ways of conceptualizing and classifying psychopathology are also possible, and selecting the most optimal approach is an empirical matter. In particular, models of psychopathology can be developed in an explicit, quantitative framework, and their ability to capture empirical data on psychopathology can be compared. To frame a discussion and review of this emerging model-based approach to understanding and classifying psychopathology, we begin with a brief history of the term and concept of comorbidity.

HISTORICAL ORIGINS OF THE COMORBIDITY CONCEPT

The comorbidity concept originated in literature on the epidemiology of medical diseases. The term was coined by Feinstein (1970). Feinstein offered a number of specific wordings to define comorbidity throughout his seminal 1970 paper, but a definition from the first sentence of the summary section provides a succinct statement of the idea he had in mind: “In a patient with a particular index disease, the term co-morbidity refers to any additional co-existing ailment” (p. 467). Interestingly, in another section of this paper, Feinstein (1970) broadens the term beyond ailments to include “such ‘non-disease’ clinical entities as: pregnancy; deliberate dieting in an effort to lose weight; and certain symptomatic reactions, such as nausea, that may occur with various therapeutic maneuvers” (p. 457). Thus, the concept Feinstein (1970) had in mind was quite broad, in the sense that comorbidity could refer to any clinically relevant phenomenon separate from the primary disease of interest that occurs while the patient is suffering from the primary disease, even if this secondary phenomenon does not qualify as a disease per se.

Generally speaking, the comorbidity concept entered the psychiatric and psychological literature much later than 1970. A citation analysis presented by Lilienfeld et al. (1994) indicates that the concept took root in the psychiatric and psychological literature starting around the late 1980s to early 1990s. This timing coincides closely with the aftermath of the development of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III) (Am. Psychiatr. Assoc. 1980) and the publication of the revised DSM-III, the DSM-III-R (Am. Psychiatr. Assoc. 1987). DSM-III was revolutionary relative to DSM-II in a number of respects, perhaps most notably in the inclusion of highly explicit operational criteria for mental disorders. The explicit nature of the definitions of mental disorders in DSM-III allowed the development of highly structured interviews that could be used to evaluate the presence of mental disorders efficiently in large groups of community research participants. In addition, the majority of mental disorder categories described in the DSM-III contained criteria specifying that a specific disorder could not be “due to” another disorder.

In the context of epidemiological data generated using structured interviews and struggles to understand how to implement the DSM-III “not due to another disorder” exclusionary criteria, the scope and magnitude of the comorbidity phenomenon became apparent. Boyd et al. (1984) provided a key contribution from this era, working with data collected as part of the multisite Epidemiological Catchment Area (ECA) project (Robins & Regier 1991). Boyd et al. (1984) first note the extensive conceptual problems inherent in attempting to operationalize the exclusionary criteria of DSM-III. For example, if panic disorder occurs only during episodes of major depression in an individual, is the panic disorder “due to” the major depression? What if these disorders simply happened to occur at the same time? Might “due to” also refer to one disorder “causing” another even if the disorders are well separated in time? Boyd et al. (1984) then proceeded to examine co-occurrence patterns across a wide variety of DSM-III disorders, without using the conceptually problematic “due to” exclusionary criteria.

They found that disorders across the nosology co-occur much more frequently than would be expected by chance.

The analysis of Boyd et al. (1984)—as well as more general concerns regarding how to implement the idea of excluding a diagnosis because it is “due to” another disorder—led to dropping many exclusionary rules in the DSM-III-R (Robins 1994). Large-scale epidemiological studies subsequent to the ECA, such as the DSM-III-R-based National Comorbidity Survey (Kessler et al. 1994) and the DSM-IV-based National Comorbidity Survey-Replication (Kessler et al. 2005), have shown unequivocally that mental disorders co-occur more frequently than would be expected by chance. Such epidemiological data are often regarded as compelling evidence that the comorbidity phenomenon is not an artifact of a specific sampling frame, especially in the sense that comorbid cases should be more common in the clinic than in the population at large, even if probabilities of seeking help for specific diagnoses are independent (a phenomenon termed “Berkson’s bias”; Berkson 1946). Indeed, in clinical settings, individuals with a single diagnosis are very rare; for example, Brown et al. (2001) found that 95% of individuals who met criteria for lifetime major depression or dysthymia in a clinical sample also met criteria for a current or past anxiety disorder.

Consistent with the extent of this phenomenon and its clinical importance, the term “comorbidity” is frequently encountered in the literature. For example, a search using the term “comorbidity” as a keyword in PsychINFO 1872 to May Week 3 2005 produced 8500 results—a nontrivial corpus of publications, given that the term did not really take root until the late 1980s–early 1990s (Angold et al. 1999, Batstra et al. 2002, Lilienfeld et al. 1994). Clearly, the phenomenon is of great interest in the psychopathology research community.

WHAT DOES COMORBIDITY MEAN?

In spite of the proliferation of literature on comorbidity, a number of fundamental issues regarding the meaning of the term persist in recent literature. A key issue pertains to the distinction between disorder concepts as applied to a specific individual and disorder concepts as applied to a sample of individuals. Although this distinction is fundamental, it is a distinction not directly encoded in the term “comorbidity.” Returning to the seminal work of Feinstein (1970), he discussed and was concerned about the relevance of comorbidity in studying disease in the population, yet his definition applies to a specific individual patient. This focus is quite sensible from the perspective of the front-line clinician, who deals not with disorder constructs as applied to groups of people, but with those constructs as applied to specific individuals. Consider an example: It is likely that a significant proportion of people who meet criteria for a prevalent mental disorder in clinical settings (e.g., major depression) are also nearsighted. This phenomenon could legitimately be termed comorbidity, following from Feinstein’s (1970) definition. Moreover, this phenomenon would be of clinical interest and importance with regard to a specific patient. As a clinician, if we encountered a patient who was clearly depressed and also found it difficult to see faraway objects clearly, the responsible course of action would be to treat the depression and to obtain a proper consult for the vision impairment.

Yet the phenomenon that has captured the interest of psychopathology researchers is different from the basic fact that any given person may legitimately qualify for more than one clinical condition. The epidemiological data on comorbidity described above do not refer simply to the fact that any given person with a disorder could also have another disorder. Instead, what is of interest to the field is that a person who meets criteria for a specific mental disorder is much more likely to also meet criteria for other mental disorders than one would expect simply by chance. That is, mental disorder constructs, as applied to groups of people, are correlated. The term comorbidity legitimately encompasses this correlational phenomenon—it allows people to have more than one diagnosis. The problem is that the term also encompasses the simple

fact that a person who meets criteria for a specific disorder could meet criteria for another disorder even if no correlation exists between the two disorders. That is, the term comorbidity does not differentiate between the idea that two legitimate diagnoses may be made in a specific individual (a phenomenon that could be described as co-occurrence) and the observation that two diagnoses are correlated or covary in a group of people.

The distinction between co-occurrence and correlation is conceptually important, and a problem noted in recent literature is that the term comorbidity could legitimately refer to either phenomenon. For example, Vella et al. (2000, p. 25) write that “comorbidity should be defined as two or more diseases, with distinct aetiopathogenesis (or, if the etiology is unknown, with distinct pathophysiology of organ or system), that are present in the same individual in a defined period of time.” This definition is closer to the idea of co-occurrence captured by Feinstein’s (1970) definition, although it also adds the provision that some evidence of underlying causal distinctiveness is needed for the term “comorbidity” to apply (cf. Lilienfeld et al. 1994, Meehl 2001). By way of contrast, in writing on the comorbidity of childhood psychopathologies, Lilienfeld (2003) restricts his use of the term to “covariation” among diagnoses across individuals rather than co-occurrence among diagnoses within individuals. None of the authors could be said to be wrong in the way they approach working with the term “comorbidity.” The problem is that the term itself is broad enough to encompass too many conceptually distinct phenomena.

For example, how does one compute the comorbidity rate for a specific sample? Working from Feinstein’s (1970) definition, one could report the percentage of persons with two specific diagnoses. The problem with this approach is that apparently impressive percentages of comorbid cases could, in theory, be compatible with both co-occurrence expected by chance and co-occurrence at rates greater than those expected by chance (i.e., correlation). Co-occurrence expected by chance is the product of the prevalences (also known as base rates) of the two disorders. For example, if the prevalence of Disorder A is 75% and the prevalence of Disorder B is 50%, 38% of the sample would have both disorders, just by chance, because $75\% \times 50\% = 38\%$. Given that, in clinical settings, the prevalence of many disorders is substantial using both unstructured and structured approaches to interviewing (e.g., major depression; Zimmerman & Mattia 1999), comorbid cases could be frequently encountered just by chance.

Yet extensive evidence shows that comorbid cases are encountered far more than would be expected by chance. This was noted early on by Boyd et al. (1984), who presented a table showing that the number of cases in their sample with two or more coexisting disorders is notably greater than would be expected by chance, whereas the number of cases with only a single disorder is notably less than would be expected by chance. The problem is that this phenomenon is typically termed comorbidity when, in fact, simply observing that some people meet criteria for more than one diagnosis could also legitimately be termed comorbidity.

A related concern emerging in recent literature relates to the prefix “co-” added to the word “morbidity.” That is, Feinstein’s (1970) definitions pertain to two diagnoses. Yet the general tendency for mental disorders to be correlated means that three or more diagnoses are not uncommon. Should terms such as “trimorbidity” or “quadramorbidity” be used to describe individuals with the requisite number of diagnoses? Inventing more terms for these complex patterns may not be very productive, yet developing a way of conceptualizing persons with complex patterns of more than two diagnoses is crucial for the field. Such persons are more frequent than expected by chance; Boyd et al. (1984) observed 22.4 times as many cases with three or more diagnoses than would be expected just by chance. These “multimorbid” cases also carry a disproportionate burden of risk for psychopathology. In the National Comorbidity Survey (Kessler et al. 1994), more than half of mental disorders in the past year occurred in people with a lifetime history of three or more diagnoses. These data are not well captured by

the term comorbidity in the sense that the term does not explicitly refer to more than two diagnoses. Interestingly, the conceptual conundrum here is not limited to mental disorders, as the term “multimorbidity” appears to be gaining influence in literature on the epidemiology of more broadly defined medical disease (Van den Akker et al. 1996) yet appears rarely in literature on mental disorders (Batstra et al. 2002).

Other commentators have also expressed concerns about the term and concept of comorbidity, and, at the same time, the importance of understanding the phenomena encompassed by the term. A fascinating interchange is found in the work of Lilienfeld et al. (1994) and commentaries on that work (Blashfield et al. 1994, Robins 1994, Rutter 1994, Spitzer 1994, Widiger & Ford-Black 1994). In addition to discussing the confusion between co-occurrence and covariation, Lilienfeld et al. (1994) argue that the term comorbidity is not very helpful in psychopathology research because it tends to reify current mental disorder constructs, implying a level of conceptual clarity that is currently lacking (e.g., that disorders are bona fide categories with well-understood and discrete etiologies and pathophysiologies). Lilienfeld et al. (1994) then suggest that the term “comorbidity” be avoided, and propose the use of the more precise terms “co-occurrence” and “co-variation” as appropriate. A number of commentators on this work were sympathetic with the need for greater precision, but felt that abandoning the term “comorbidity” would be premature and even perhaps counterproductive. Rutter (1994), for example, argued that comorbidity should serve as an impetus to research on the validity of current diagnostic constructs, and that abandoning the term could lead to the unintended consequence of stopping such research. Similarly, Spitzer (1994) regarded comorbidity as a reasonable label for co-occurring entities that may not rise to the conceptual level of bona fide categories with clear-cut etiologies and pathophysiologies—not only in psychiatry, but in medicine more generally—and therefore, that Lilienfeld and colleagues’ concerns were misplaced.

Nevertheless, the issues raised in the Lilienfeld et al. (1994) exchange, and dissatisfaction with the comorbidity concept, resonate throughout more recent literature. Maj (2005a,b) suggests that the fact that various mental disorders rarely occur in isolation could be viewed as evidence that comorbidity is an artifact of current diagnostic systems imposing categorical distinctions that do not exist in nature. Along these lines, Meehl (2001) suggests that the term “comorbidity” would be most meaningfully applied to taxonic categorical conditions, where distinct and discrete latent structures underlie the two comorbid conditions. Bogenschutz & Nurnberg (2000) emphasize the importance of sorting through these issues to clarify thinking about diagnosis, noting that comorbidity among certain categorical mental disorders (e.g., major depression and posttraumatic stress disorder) may be better understood from a dimensional framework. Batstra et al. (2002) note that bivariate statistics such as odds ratios tend to be used in studying comorbidity among mental disorders, even though the phenomenon appears to be multivariate in nature and requires a statistical approach capable of mapping the concept of multimorbidity. Van Praag (1996, p. 132) suggests that the term “comorbidity” “conceals more than it clarifies, if used without further qualification,” noting that the basic data on comorbidity could be compatible with a number of diverse interpretations, a situation indicating a need to build and test more specific models of specific forms of comorbidity.

Concerns have also been raised about comorbidity in everyday clinical practice. Kaplan et al. (2001) note that few children represent prototypical cases of specific disorders, yet describing a child as “comorbid” may be less helpful in clinical case conceptualization and in parent communication than conceptualizing and communicating about more general mechanisms that may unite putatively distinct disorders (e.g., atypical brain development). In an article on comorbidity among child and adolescent forms of psychopathology, Jensen (2003) notes that many studies exclude children with comorbid disorders, rendering the relevance of those studies to the typical clinical case unclear.

In sum, the breadth of the phenomena that could be termed “comorbidity” suggests a concept in need of thoughtful refinement. Indeed, Lilienfeld (2003) describes a personal communication with Feinstein in which he was reported to express dissatisfaction with the overuse of the term. Still, the basic phenomenon that has captured the interest of the field under the comorbidity rubric seems clear and important: Mental disorders are significantly correlated. That is, meeting criteria for one disorder predicts meeting criteria for others. The challenge, then, is to understand why this happens and what it means for how we might best conceptualize and understand psychopathology. This would involve delineating models of the comorbidity among mental disorders (see, e.g., Lilienfeld 2003, Lyons et al. 1997, Maser & Cloninger 1990, Rutter 1997) and determining which models best capture the empirical data documenting significant correlations among diverse disorders, an endeavor that should help in revealing the meaning of the comorbidity phenomenon.

MODELING COMORBIDITY

Many of the controversies surrounding the concept of comorbidity can be resolved by being explicit about links between data on comorbidity among mental disorders and conceptual models of those data. Papers by Klein & Riso (1993) and Neale & Kendler (1995) have provided the most systematic characterization of different comorbidity models to date. Klein & Riso (1993) originally described a comprehensive set of comorbidity models, which Neale & Kendler (1995) later elaborated and formalized in a quantitative manner. These models, characterized by Klein & Riso (1993) and Neale & Kendler (1995) (hereafter referred to as KRNK models), are bivariate; that is, they involve only two disorders considered simultaneously. As noted above, however, the comorbidity phenomenon is perhaps better described as a multimorbidity phenomenon in the sense that patterns of association among mental disorders involve multiple disorders across the current nosology (cf. Batstra et al. 2002). For this reason, it is also important to consider multivariate models, which involve more than two disorders simultaneously. Here, we first briefly summarize the bivariate KRNK models and then discuss multivariate models.

BIVARIATE COMORBIDITY MODELS

Associated Liabilities Models

A number of the KRNK models can be treated as subtypes of a single, more general model that we refer to here as the associated liabilities model. A liability is an indirectly observed or latent propensity to develop directly observed or manifest disorders. This model, which is illustrated in Figure 1a, posits that each disorder is influenced by a latent liability factor and that these liability factors are correlated. The latent liability factors A and B are represented by the circles at the top of Figure 1a, and the manifest or observed mental disorders 1 and 2 are represented by the squares at the bottom of Figure 1a; liability factor A corresponds with disorder 1, and liability factor B corresponds with disorder 2. The degree of correlation between the liability factors, r , represented by the curved line at the top of Figure 1a, defines three distinct subtypes of associated liabilities models. Under the chance model, the liability factors are uncorrelated (i.e., $r = 0$), and comorbid cases occur purely by chance. Under the correlated liabilities model, the liability factors are correlated at some level between zero and one (i.e., $0 < r < 1$), and comorbid cases reflect the correlation between these liabilities. Under the alternate forms model, the liability factors are perfectly correlated (i.e., $r = 1$), and the two observed disorders as well as comorbid cases all represent alternate forms of the same condition.

Multiformity Models

Multiformity models represent heterogeneity in the expression of liability, i.e., the possibility of multiple pathways from same liability to different manifestations of that liability. These

models (represented in Figure 1*b*) posit that the liability factors A and B are independent and uncorrelated, but that both liability factors can cause symptoms of both disorders 1 and 2. This situation is represented in Figure 1*b* by the arrows connecting both liability factors to both disorders. An individual who is elevated on one liability factor might meet criteria for two disorders, because a single liability can be expressed through multiple disorders. Because each liability can be expressed as either disorder, there are effectively three ways of being comorbid—by being elevated on one liability factor, the other liability factor, or both. Comorbid cases represent a mixture of individuals, some of whom are elevated in one liability factor, some of whom are elevated on the other liability factor, and some of whom are elevated on both.

Causation Models

The KRNK causation models posit that one disorder may directly cause another disorder (Figure 1*c*). Under causation models, comorbidity results because of the direct influence of one disorder on the development of the other disorder. In directional causation models, one disorder causes the other. In the reciprocal causation model, in contrast, both disorders may cause one another. Causation models differ from the associated liabilities models and the multiformity models in that comorbidity results not from the nature or expression of liability patterns, but rather from the direct influence of one disorder on another. Note that in Figure 1*c*, there are no latent liabilities A and B, and the disorders 1 and 2 are connected directly as opposed to through the latent liabilities portrayed in Figures 1*a* and 1*b*.

Independence Model

Under the independence model, comorbid disorder reflects an independent condition, separate from the other disorders. Each disorder is influenced by its own liability factor, and comorbid disorder is itself also influenced by its own liability factor, distinct from the liability factors influencing other disorders. Under this model, comorbidity does not represent the combined presence of two disorders, but rather a third distinct disorder. This model is illustrated in Figure 1*d*. Note that in this figure, there are three liability factors and three manifest disorders, all mutually uncorrelated. Disorder 1 is influenced by liability factor A, disorder 2 is influenced by liability factor B, and the disorder labeled “1 & 2,” to signify that it presents with the symptoms of disorders 1 and 2 simultaneously, is influenced by the third independent liability factor, C.

Spurious Association Models

A final set of KRNK models can be generally described as spurious association models. Under these models, some external variable or set of variables creates spurious associations between disorders. In the sampling bias model, for example, sampling methods bias selection of comorbid cases. This could occur if comorbid cases are oversampled because individuals with a greater number of disorders have more opportunities to be selected for study (e.g., Berkson 1946). In the population stratification model, similarly, comorbid cases occur because distinct liabilities for two disorders nonetheless segregate nonrandomly in the population due to extraneous causes. This could occur if certain combinations of risk factors, otherwise independent, are more commonly observed in certain groups than in others, e.g., particular socioeconomic groups.

MULTIVARIATE COMORBIDITY MODELS

Bivariate models are important and useful theoretically because they focus on the fundamental elements of comorbidity: two disorders and their combination. In evaluating patterns of comorbidity, however, it is often useful to extend analysis to multivariate models, where more than two disorders are considered simultaneously. Multivariate models, for instance, are more comprehensive in providing explanations of comorbidity than are bivariate models. In

incorporating a greater number of disorders, multivariate models elucidate important implications of different comorbidity models in a way that bivariate models do not.

Most multivariate comorbidity models can be treated as extensions of bivariate models to a greater number of disorders. In extending such models to include more disorders, however, hybrid models can be specified that would not be possible in the bivariate case. This flexibility allows multivariate models to provide more comprehensive explanations of comorbidity than bivariate models. Figure 1e illustrates this point. The comorbidity model represented by the path diagram in Figure 1e is a hybrid of the associated liabilities and multiformity models. Disorders 1–3 reflect alternate forms of the first liability A, and disorders 4–6 reflect alternate forms of the second liability B, suggesting that comorbidity between disorders within each group is best explained by an alternate forms model. However, the two liabilities are correlated, which suggests that comorbidity between disorders in the first group and second group is best explained by a correlated liabilities model. Moreover, disorder 3 is influenced by both liability distributions directly, suggesting that comorbidity between disorder 3 and other disorders might be best explained by a multiformity model that takes into account both liabilities, A and B. The general point is that the multivariate model represented in Figure 1e unifies a number of bivariate models into a single integrated, albeit rather complex, account of the multimorbidity among six disorders.

In extending comorbidity models to multiple disorders, it is often possible to discover implications of a given model that might not be apparent when using a bivariate model. One particularly important implication of any given comorbidity model is its parsimony or lack thereof. In general, more parsimonious models are to be preferred over more complex models, as they can explain more observations with fewer assumptions. Mathematical theory indicates that, statistically speaking, more parsimonious models are more likely to be true population models than less parsimonious models (Vereshchagin & Vitanyi 2004).

Multivariate models often elucidate the importance of parsimony in a way that bivariate models do not. Consider, for example, the correlated liabilities and alternate forms models. In the bivariate case, the two models are equally complex and interchangeable, having the same number of parameters and producing the same fit. In the multivariate case, however, the correlated liabilities model becomes much more complex. Assuming a unique liability for each disorder, the correlated liabilities model includes a parameter representing every correlation between each combination of disorder. However, with only one liability, the alternate forms model includes only one parameter for each disorder, representing the influences of the single liability on each disorder. The complexity of the multivariate correlated liabilities model therefore increases with the number of disorders much more quickly than the multivariate alternate forms model. The correlated liability model in this way is much more complex than the alternate forms model in the multivariate case.

Multivariate models therefore not only are more flexible than bivariate models in providing explanations for comorbidity, but they also elucidate the parsimony of those explanations in a way that bivariate models do not. Models that seem equally complex in the bivariate case may differ a great deal in the multivariate case. As disorders are added to the model, one model may become overly complex relative to another model that provides the same explanatory power with fewer assumptions.

EVALUATING COMORBIDITY MODELS

The foregoing discussion shows how structural modeling can provide a powerful approach to understanding patterns of comorbidity by making various theoretical conceptions of the meaning of comorbidity explicit. The next step is to apply these models to data. In pursuing this step, it is important to delineate the conditions in which the models can be effectively

compared. Certain models may be difficult to distinguish due to similarities in the predictions they make, and may require special study designs to be effectively compared.

Key simulation work in this area has been reported by Rhee and colleagues (Rhee et al. 2003, 2004, 2005). Rhee and her colleagues have evaluated the statistical power to distinguish between different bivariate comorbidity models, and have concluded that different comorbidity models can be distinguished well in many circumstances, with some caveats. First, as might be expected, the authors have concluded that similar comorbidity models—e.g., different subtypes of comorbidity models, such as the directional causation and reciprocal causation models shown in Figure 1c—are more difficult to distinguish than comorbidity models that are structurally very different, such as the alternate forms and directional causation models. Second, the authors have concluded that it is sometimes difficult to distinguish between different comorbidity models when the prevalences of one or both of the disorders is very low or when correlations between liabilities are small. Finally, the authors have concluded that very large samples may be required to obtain adequate power to discriminate between different comorbidity models. The authors did not evaluate multivariate models, so it is unclear how well their results would generalize to models including multiple disorders simultaneously.

The studies of Rhee et al. (2003, 2004, 2005) underscore the importance of study design in distinguishing between different accounts of comorbidity. Rhee et al. (2003) noted, for example, that longitudinal designs should be particularly useful in distinguishing different causation models from one another or from other types of models—e.g., the different directional causation models from each other, or from the reciprocal causation models. Biometric study designs (e.g., twin or family designs) are also useful in delineating the relationships between disorders. Many models that are indistinguishable in simple phenotypic cross-sectional designs—e.g., the correlated liabilities and alternate forms models—can be distinguished in biometric designs due to the addition of information about comorbidity patterns across relatives (Neale & Kendler 1995).

The conclusions of Rhee et al. (2003, 2004, 2005) are echoed by Simonoff (2000), who explored the ability to distinguish between different bivariate comorbidity models using behavior genetic designs. Supporting Rhee et al.'s (2005) conclusions, Simonoff (2000) demonstrated that very large samples are sometimes required to distinguish between various comorbidity models. Given that prohibitively large samples are sometimes required to distinguish between models using direct statistical comparisons, Simonoff (2000) argued that other criteria might be necessary to select between different comorbidity models. The plausibility of various models may differ, for example, based on temporal relationships between disorders or other considerations. Other forms of evidence, from experiments or other designs, may also support one model over another and should be considered when evaluating accounts of comorbidity.

APPLICATIONS OF COMORBIDITY MODELS

Bivariate Models

Although there is an extremely large literature on bivariate relationships between disorders, relatively few studies have explicitly compared multiple models of comorbidity within a KRNK framework. Among different forms of comorbidity, depression and anxiety disorder comorbidity seems to be the most frequently modeled. Perhaps the most comprehensive review of models of comorbidity between depression and anxiety disorders was provided by Middeldorp et al. (2005), who reviewed twin and family studies of depression and anxiety disorder in the framework of KRNK models. Middeldorp et al. (2005) concluded that shared genetic liability can explain much of the comorbidity between depression and the anxiety disorders.

Another example of a study comparing bivariate KRNK models was provided by Johnson et al. (2004), who compared various KRNK models of comorbidity between smoking and depression. In their analyses, the correlated liabilities and reciprocal causation models provided equal and optimal fit. However, as the parameter estimates from the reciprocal causation model were not consistent with comparable estimates from the directional causation models, the authors concluded that the correlated liabilities model provided the most compelling explanation for the data. The authors demonstrated, furthermore, that familial associations between smoking and depression accounted for approximately 73% to 95% of the total variance shared between the two problems.

Multivariate Models

In addition to literature on bivariate comorbidity models, a number of studies have examined multivariate comorbidity models, working from an associated liabilities framework. The idea behind this work has been to search for the underlying latent liability factors that give rise to comorbidity across numerous mental disorders. These studies have generally converged on a specific hierarchical model for comorbidity between common forms of psychopathology. This hierarchical model includes two superordinate liabilities: internalizing, a general liability toward negative-affect-laden mood and anxiety disorders; and externalizing, a general liability toward disinhibitory disorders such as substance use disorders and antisocial behavior disorders (Achenbach 1966, Krueger 1999, Vollebergh et al. 2001). Internalizing and externalizing are often found to be correlated, and the internalizing liability often bifurcates into two subordinate liabilities, distress and fear (cf. Watson 2005).

We conducted a meta-analysis to summarize the existing literature on this multivariate associated liabilities model for the current review. This meta-analysis comprised published studies of multivariate comorbidity models applied to DSM-defined dichotomous mental disorders in large, population-representative samples. Five studies were included in the meta-analysis: a population-based study of the Virginia Twin Registry (Kendler et al. 2003), a study based on the National Comorbidity Survey (Krueger 1999), a population-based study in the Netherlands (Vollebergh et al. 2001), a population-based study in New Zealand (Krueger et al. 1998), and a study based on the National Comorbidity Survey Replication (Kessler et al. 2005). Data obtained from 23,557 research participants were represented. The 11 diagnoses modeled in multiple samples across those five studies were included in the meta-analysis. We fit structural equation models to tetrachoric correlation matrices reported in the five studies, using maximum likelihood multiple-groups methods, as implemented in the computer program Mx (Neale et al. 2003).

Table 1 presents model fit statistics for the meta-analyses, in particular, the Bayesian Information Criterion, an index that takes statistical parsimony into account as described above (Rissanen 1983). The hierarchical internalizing-externalizing model fit better than alternative models, such as a one-factor, a correlated two-factor model comprising only internalizing and externalizing factors, and a correlated four-factor model comprising separate affective, anxiety, substance use, and antisocial behavior factors. It provides exactly the same fit as a correlated three-factor model, being a reparameterization of the latter.

Figure 2 presents parameter estimates from the best-fitting model according to the meta-analytic multiple-groups confirmatory factor analysis. This model is essentially the same model identified in previous studies, comprising the superordinate internalizing and externalizing liabilities. Internalizing and externalizing are correlated, and internalizing bifurcates into two separable but highly correlated liabilities, labeled distress and fear. Distress is a liability to major depression, dysthymia, and generalized anxiety disorder, and fear is a liability to more paroxysmal internalizing disorders such as panic disorder and the phobic disorders.

DEVELOPING A MODEL-BASED CONCEPTUALIZATION OF PSYCHOPATHOLOGY

The goal of the foregoing section was to illustrate how controversies surrounding the concept of comorbidity can be resolved by linking data on comorbidity among mental disorders with conceptual models of those data. Recent applications of the KRNK framework to bivariate comorbidity patterns have converged on correlated liability models (Johnson et al. 2004, Middeldorp et al. 2005), although it is also important to note that many pairs of disorders have not been subjected to the rigorous treatment available in the full KRNK framework. In addition, our meta-analysis of multivariate studies of comorbidity converged on the model portrayed in Figure 2, in which comorbidity is understood as a function of underlying liability constructs. It is important to note, however, that alternate models stemming from the KRNK framework could be extended to the multivariate context. Consideration of such models, as well as various hybrid models (e.g., the model portrayed in Figure 1e), could further refine our understanding of the meaning of comorbidity. Keeping these limitations in mind, however, a reasonable interpretation of the existing literature is that the extensive comorbidity among mental disorders reflects the existence of a smaller number of liability constructs that underlie multiple disorders. The remainder of our review focuses on this emerging liability spectrum conceptualization of psychopathology—how it resolves conceptual conundrums associated with the comorbidity concept, and points to new directions in conceptualizing psychopathology.

Nosological Implications of a Liability-Spectrum Model

A liability-spectrum conceptualization of psychopathology emerges from empirical work aimed at understanding the extensive comorbidity among mental disorders defined in official nosologies. The consensual definitions of categories of mental disorder described in DSM-III (Am. Psychiatric Assoc. 1980) and its offspring provided a fundamental first step for the development of this conceptualization because work with those categories reveals the magnitude, scope, and patterning of the comorbidity phenomenon. Nevertheless, a liability-spectrum model also points toward some evolutionary steps in the ways we think about psychopathology and its classification.

Although liability constructs per se are not formally incorporated into the DSM, the section headings of the DSM are often interpreted as classificatory rubrics. For example, DSM-IV-TR (Am. Psychiatric Assoc. 2000) contains separate sections to describe mood disorders and anxiety disorders, which are often regarded as two distinct types of mental disorder. The model portrayed in Figure 2 suggests a specific data-based organizational scheme that is somewhat distinctive from the scheme portrayed in the section headings of DSM-IV-TR. The broad internalizing liability impacts disorders transcending the putative distinction between mood and anxiety disorders (cf. Acton et al. 2004), with a subdivision in which generalized anxiety disorder shares more liability in common with mood disorders than with anxiety disorders (cf. Watson 2005). In addition, the broad externalizing liability encompasses not only disorders currently classified as substance-related, but also the Axis II construct of antisocial personality disorder (divided in Figure 2 into the child conduct disorder and adult aspects of antisocial personality disorder; cf. Krueger et al. 2005). The Figure 2 model thereby suggests some reshuffling of constructs described in the DSM to better reflect their empirical organization, keeping in mind the fact that the vast majority of mental disorders described in the DSM could not be included in the Figure 2 model because the relevant data were not available. However, the model-based perspective on understanding comorbidity described in this review could be applied to other constructs described in the DSM (given the requisite data), and this endeavor could provide the scaffolding for a comprehensive empirically based system for classifying psychopathology.

In addition, a liability-spectrum model of psychopathology suggests some evolutionary steps in the way we think about specific mental disorders. Specific mental disorders are often thought of as discrete and separate entities, but this way of thinking has been repeatedly challenged by the scope of the comorbidity phenomenon, as described throughout literature reviewed earlier. The model in Figure 2 addresses these concerns by reconceptualizing specific mental disorders as alternative manifestations of underlying liabilities. The shift in emphasis here is subtle but conceptually important. The idea is not that the distinctions between specific disorders are necessarily unimportant, but rather, that psychopathology is organized hierarchically, as portrayed in Figure 2 (cf. Krueger & Piasecki 2002, Lilienfeld 2003, Weiss et al. 1998). Specific mental disorders result from more general overarching liabilities as well as features distinguishing specific manifestations of those liabilities. In this conceptualization, varieties of psychopathology are distinguished in a continuous, graded fashion.

Structural Aspects of a Liability-Spectrum Model: Discreteness and Continuity

Along these lines, an emerging issue in the modeling of comorbidity is the discreteness versus continuity of liabilities to disorder. The KRNK models, as well as the methods used in our meta-analysis, treat underlying liability as a continuous phenomenon, with individuals varying along a continuous, graded range of liability to disorder. Another tractable possibility is to treat the liabilities as discrete, with individuals being members of discrete classes or groups of individuals. Under the former conceptualization, liability represents a continuum of risk to disorder; under the latter conceptualization, liability represents types or categories of risk to disorder. An interesting case of the latter model is a model with as many discrete liabilities as there are manifest disorders, i.e., a model in which each manifest mental disorder is a discrete and categorical latent entity.

Methodological advances suggest that discrete and continuous models of liability can be statistically distinguished (Markon & Krueger 2004, Waller & Meehl 1998). By formulating discrete and continuous accounts of liability within a common modeling framework, for example, they can be meaningfully compared and evaluated (Markon & Krueger 2004). This approach was illustrated in two studies of liability toward disorders in the externalizing spectrum: one involving a sample of adult parents from an ongoing twin-family study (Krueger et al. 2005), the other involving a large, population-representative sample of adults in the United States (Markon & Krueger 2005). In both studies, a continuous normal model of liability provided a better-fitting account of multivariate patterns of comorbidity than did various discrete models of liability, indicating that externalizing disorders reflect a graded continuum of liability rather than discrete categories. Notably, models positing categorical and separate liabilities for each manifest mental disorder did not fit well in either study, indicating that this conception of externalizing mental disorders as separate discrete categories was not empirically accurate.

Nevertheless, discrete and continuous models of liability are not necessarily mutually exclusive (cf. Kraemer et al. 2004), and hybrid models may prove helpful in various domains (Muthen 2002). It is possible, for example, that certain disorders reflect discrete forms of liability, while other disorders reflect continuous forms of liability. It is also possible that liabilities to mental disorder reflect mixtures of continua, with individuals being members of continuously distributed liability groups (Uebersax & Grove 1993). Under such a scenario, individuals are characterized by categories of risk, but in each category, liability is continuously distributed. The general point is that the continuity and/or discreteness of psychopathology need not be a matter of a priori preference; this perennial debate can be resolved empirically in a model-fitting framework.

Etiological Aspects of a Liability-Spectrum Model: Behavior Genetic Modeling of Comorbidity

A model-fitting framework can also help in evaluating the etiological bases of liability constructs. In particular, evidence in favor of a liability-spectrum framework for understanding comorbidity would be enhanced if liability constructs identified phenotypically were also etiologically coherent. Kendler et al. (2003) reported the most comprehensive multivariate behavior genetic study addressing this issue. These authors noted that a number of behavior genetic studies of comorbidity between pairs of disorders have appeared in the literature, but few studies have examined multimorbidity across an extensive array of mental disorders. To fill this gap, Kendler et al. (2003) modeled multimorbidity among a diverse array of ten mental disorders, transcending both the internalizing and externalizing spectra. The structure of genetic risk they documented closely resembles the model in Figure 2. In particular, their data supported a genetic basis for the coherence of both the internalizing and externalizing spectra, as well as a genetic basis for the distinction within the internalizing spectrum between the distress (or “anxious-misery”) and fear subliabilities. Their data also supported a hierarchical conceptualization of comorbidity, as a number of specific disorders in their analysis (e.g., alcohol dependence), although significantly linked to broad liability factors, were also distinguished from each other by genetic factors unique to each disorder.

Psychological Aspects of a Liability-Spectrum Model: The Role of Personality in Psychopathology

Liability constructs such as those portrayed in Figure 2 bear a notable resemblance to personality traits. Personality traits and liability constructs are both latent entities that explain the psychological coherence of specific individual difference domains. Empirical evidence regarding the connections between personality and psychopathology supports this connection and clarifies the psychological aspects of comorbidity patterns. Disorders in the internalizing spectrum are consistently linked to personality traits in the broad domain of negative emotionality or neuroticism, and disorders in the externalizing spectrum are consistently linked to personality traits in that domain, as well as to traits in the broad domain of disinhibition (a domain encompassing disagreeableness and a lack of conscientiousness; see, e.g., Clark 2005, Krueger 2005 for recent reviews). Connecting the personality and psychopathology domains, given normative levels of disinhibition, negative affect appears to confer risk for internalizing disorders, whereas negative affect in the presence of disinhibition confers risk for externalizing disorders (see also Acton & Zodda 2005 for a related perspective). Indeed, personality traits have been shown to account directly for comorbidity patterns in a manner consistent with this psychological interpretation. Khan et al. (2005) showed that a substantial percentage of the comorbidity within the internalizing spectrum and between internalizing and externalizing disorders was accounted for by neuroticism, whereas variation in both neuroticism and novelty seeking (a disinhibitory personality trait) accounted for a notable percentage of the comorbidity within the externalizing spectrum.

CONCLUSIONS

Comorbidity has been a persistent puzzle in psychopathology research. In this review, we have suggested that the puzzle of comorbidity is in the process of being solved by research fitting explicit quantitative models to comorbidity data. A body of existing research in this vein supports a liability spectrum model of comorbidity. In this framework, the tendency for mental disorders to be comorbid is neither artifact nor nuisance. It is instead a predictable consequence of the involvement of common liability factors in multiple disorders. Work on the classification of psychopathology, such as the processes that are leading toward DSM-V, could benefit from taking this framework explicitly into account. Research on psychopathology could benefit from this framework by shifting focus toward the study of liability constructs along with specific

manifestations of liabilities in specific mental disorders. Much work remains to be done to understand if this framework is also applicable to the numerous psychopathology constructs that have yet to be explicitly modeled. Nevertheless, we are optimistic that quantitative modeling of relevant data will eventually lead to a comprehensive system for classifying psychopathology that is empirically based and useful both in research and in the clinic.

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Figure 1. Bivariate and multivariate comorbidity models: (a) associated liabilities model, (b) multifactor model, (c) causation models, (d) independence model, and (e) a hypothetical multivariate model. Note that models are not necessarily mathematically identified as shown; they may require additional parameter constraints or may require appropriate data (e.g., longitudinal or family) to be tested.

Figure 2.
Path diagram for best-fitting meta-analytic model.

Table 1

Meta-analytic model fit statistics

Model	log(L)	k	BIC
1-factor	-15552.02	11	15607.39
2-factor correlated	-10477.27	12	10537.67
3-factor correlated	-6878.53	14	6949.00
4-factor correlated	-7819.48	17	7905.05
Hierarchical	-6878.53	14	6949.00

Note: $\log(L)$ is the log-likelihood associated with the model; k , the number of parameters; BIC, the Bayesian Information Criterion. Lower values of BIC indicate better fit. The 3-factor and hierarchical models are reparameterizations of each other and produce equivalent fit statistics.