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Comorbidity: A network perspective

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Abstract: The pivotal problem of comorbidity research lies in the psychometric foundation it rests on, that is, *latent variable theory*, in which a mental disorder is viewed as a latent variable that *causes* a constellation of symptoms. From this perspective, comorbidity is a (bi)directional relationship between multiple latent variables. We argue that such a latent variable perspective encounters serious problems in the study of comorbidity, and offer a radically different conceptualization in terms of a *network approach*, where comorbidity is hypothesized to arise from direct relations between symptoms of multiple disorders. We propose a method to visualize comorbidity networks and, based on an empirical network for major depression and generalized anxiety, we argue that this approach generates realistic hypotheses about pathways to comorbidity, overlapping symptoms, and diagnostic boundaries, that are not naturally accommodated by latent variable models: Some pathways to comorbidity through the *symptom space* are more likely than others; those pathways generally have the same direction (i.e., from symptoms of one disorder to symptoms of the other); overlapping symptoms play an important role in comorbidity; and boundaries between diagnostic categories are necessarily fuzzy.

Keywords: comorbidity; complex networks; generalized anxiety; latent variable models; major depression

1. Introduction

If suffering from a single mental disorder is bad, suffering from multiple mental disorders (i.e., *comorbidity*) is worse. Compared to suffering from a single mental disorder, comorbidity is consistently associated with a greater demand for professional help, a poorer prognosis, greater interference with everyday life, and higher suicide rates (e.g., Albert et al. 2008; Brown et al. 1995; Schoevers et al. 2005). Also, among people who meet diagnostic criteria for one mental disorder, approximately 45% receive additional diagnoses (e.g., Kessler et al. 2005b). Thus, comorbidity is a widespread and serious problem, the underpinnings of which need to be unraveled. Indeed, the comorbidity issue has been studied extensively in the past decades (e.g., Anderson et al. 1987; Angold et al. 1999; Boyd et al. 1984; Brown et al. 2001; Kashani et al. 1987; Kessler et al. 1994; 2004; 2005a; Low et al. 2008; Merikangas et al. 1998; Moffitt et al. 2007; Neale & Kendler 1995).

However, although considerable progress towards furthering our understanding of comorbidity has been made, some pivotal questions remain unanswered. Probably the most crucial question is *what* we observe when two disorders covary: a genuine phenomenon that is independent of our diagnostic criteria, measurement scales, and measurement models, or (in part) an artifact of the structure of these criteria and models (e.g., see Borsboom 2002; Neale & Kendler 1995)? The former possibility holds that a genuine source of comorbidity rates exists. As such, the disorders *themselves* are comorbid, which *causes* the symptoms of such comorbid disorders to correlate. The latter possibility holds that comorbidity is produced by the way we empirically identify these disorders; for instance, because disorders often share a number of symptoms, which leads to an artificially increased comorbidity rate. Thus, in this view, comorbidity is largely an artifact of the diagnostic system.

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In this article, we argue that these possibilities are not exhaustive. Specifically, we argue that comorbidity is not an artifact. However, we do contend that comorbidity, as it has been studied so far, *is* dependent on the way we psychometrically portray disorders and comorbidity between them: namely, with a latent variable model (e.g., factor models, item response models). Within this psychometric framework, comorbidity is generally conceptualized as a (bi)directional relationship between two latent variables (i.e., disorders) that underlie a set of symptoms. In our view, there are good reasons to doubt the validity of the psychometric assumptions that underlie this approach. We discuss these reasons and propose an alternative conceptualization of the relation between symptoms and disorders that offers a natural way of explaining comorbidity.

The central idea is that disorders are *networks* that consist of *symptoms* and *causal* relations between them. In a nutshell, what binds, say, the set of depression symptoms, is that they are thus connected through a dense set of strong causal relations. With regard to comorbidity, such a *network approach* presents a radically different conceptualization of comorbidity, in terms of direct relations between the symptoms of multiple disorders.

In contrast to existing perspectives, it is inappropriate to say that the symptoms *measure* the disorder in question. The reason is that the presence of direct causal relations between symptoms contradicts the essential assumptions that underlie psychology's main class of measurement models (latent variable models; e.g., Borsboom 2005; 2008; Borsboom et al. 2003). In fact, a network approach nullifies the need to invoke latent variables as an explanation of the covariance between symptoms. In a network approach, the relation between symptoms and disorders (or, more generally, test scores and constructs) should not be viewed as one of *measurement*, but as one of *mereology*: The symptoms do not measure the disorder, but are part of it (see also Markus [2008] for a discussion of the role of mereology and causality in statistical modeling). This is consistent with McGrath's (2005) observation that theoretical terms in psychology, such as "depression" may often refer to complex constellations of variables, rather than to a single latent structure.

Hence, it is likely that comorbidity's true colors are obscured by methodological problems that spring from the assumptions underlying such techniques. The specifics of those problems vary, but all bear one striking resemblance: they are at least in part attributable to the notion that one can focus on *diagnoses* in current comorbidity research, because diagnoses serve as reliable proxies for the latent variables that supposedly underlie them. In this article, we provide an in-depth discussion of these problems and show that the network approach avoids them.

The structure of this article is as follows. First, we introduce the network approach by contrasting it to the latent variable model. We subsequently propose an integrative way to visualize comorbidity as a symptom network, and discuss the basic features of an empirical network for *major depressive disorder* (MDD) and *generalized anxiety disorder* (GAD), based on data from the National Comorbidity Survey Replication[1] (NCS-R) (Kessler et al. 2004; 2005a; 2005b). Then, we discuss three additional methodological problems that characterize current comorbidity research and argue that adopting a network approach may help in answering questions that are, in our view, crucial when painting an accurate picture of comorbidity: How important are symptoms that overlap between two disorders as sources of comorbidity? Can we identify symptoms of a disorder that put someone at more risk of developing a second disorder compared to other symptoms? Is there an order in which people generally develop one particular disorder first and another disorder second?

2. Mental disorders: Networks of directly related symptoms instead of latent variables

Measurement models used in clinical and personality research have one thing in common: the assumption that there is some attribute we cannot observe directly (i.e., is "latent") – MDD or extraversion, for instance – and therefore, must be *measured indirectly* through the presence or absence of certain observable variables (e.g., MDD is measured by depressed mood and extraversion is measured by party-going behavior; McCrae & Costa 2008; see Michell [2005] for a detailed explanation of measurement in science). In doing so, *latent variable models* are consistent with the hypothesis that the latent attribute has causal relevance for the observed values of symptoms (e.g., see Borsboom 2008; Borsboom et al. 2003; 2004; Hood 2008): In this view, for instance,

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depression (i.e., the latent attribute) *causes* the occurrence of symptoms such as fatigue.

In line with this idea, it is commonly hypothesized that comorbidity arises due to some direct relation between two latent variables; for example, a substantial correlation as depicted in Figure 1 (e.g., MDD and GAD; Neale & Kendler 1995). Some theorize even further, and hypothesize that a direct relation between two latent variables actually reflects the existence of a "super disorder" – for example, in models in which the super disorder "negative affect" causes a variety of mental disorders (e.g., depression) which, in turn, cause observable symptoms (e.g., see Barlow et al. 2004). In accordance with both views on comorbidity, current comorbidity research mainly focuses on diagnoses as proxies of the latent disorders and computes tetrachoric correlations or odds ratios between those proxies. Although this methodology has yielded important insights (e.g., Brown et al. 2001; Kessler et al. 1994; 2005b; Merikangas et al. 1998; Moffitt et al. 2007), the latent variable model may not always offer the best psychometric perspective to conceptualize mental disorders (see also Borsboom 2008).

To see this, it is useful to consider the essence of latent variable modeling, the *common cause* hypothesis, in more detail. The common cause hypothesis posits that a latent variable causes its observable indicators. If one adopts this hypothesis for a particular set of variables, then one has to accept an important consequence: *The observable indicators cannot be directly related*; that is, if a single common cause is held responsible for the occurrence of a particular set of variables, then covariation between those variables is entirely attributable to the common cause. It is important to note here that we are referring to the *psychometric* as opposed to a *clinical* interpretation of a latent variable model. In the clinical interpretation, clinicians adhere to the existence of a latent variable while at the same time acknowledging direct relations between symptoms. In a strict psychometric sense, a latent variable model does not allow for many direct relations since the majority of covariance between symptoms needs to be explained by the common cause. As such, psychometric latent variable models imply that correlations between observable indicators are, in a nontrivial sense, spurious. When statistically modeling the relationship between a hypothesized latent variable and a set of indicators, the fact that the indicators cannot be directly related results in the statistical assumption of *local independence* (such assumptions are made, for instance, in the models used in Aggen et al. [2005], Hartman et al. [2001], and Krueger [1999]): when fitting a latent variable model to observed data, any two indicators are conditionally independent given the latent variable (Lord & Novick 1968). As such, local independence is a statistical consequence of adopting the hypothesis that a common cause structure gave rise to the associations in the data.

In our view, a common cause structure is unlikely to hold for symptoms of mental disorders. For instance, consider "sleep disturbances" and "fatigue," both of which are *DSM-IV* symptoms of MDD (see *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; American Psychiatric Association 1994). If one adopts the common cause hypothesis, a high positive correlation between these symptoms is entirely due to the common influence of the latent variable, MDD. It is questionable whether this is plausible. For instance, a direct causal relationship between those symptoms is likely to hold in at least a subset of people who experience them: If you don't sleep, you get tired. Another example: Is it plausible to assume that GAD necessarily causes both chronic worry and a difficulty to concentrate? It may well be that a direct causal relationship exists between these symptoms: the more you worry, the more difficult it is to concentrate at other things.

Thus, it appears likely that latent variable models do not optimally conceptualize the relationship between mental disorders and their symptoms. This is not to say we object to the notion that symptoms of various disorders tend to cluster together in predictable ways and that, as such, disorders may be pragmatically useful to denote such clusters (e.g., see Hartman et al. 2001). However, we do suggest that mental disorders may not explain covariation between symptoms in the way a latent variable model pictures the situation. If this is so, then even though the application of latent variable modeling may have considerable instrumental utility (e.g., in facilitating predictions or gauging rough differences between people), one cannot plausibly say that the symptoms

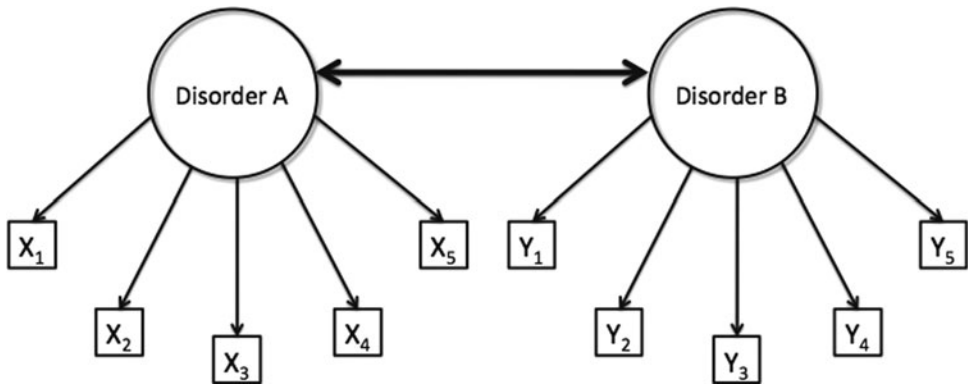

Figure 1. A model of comorbidity between disorders A and B, under the standard assumptions of latent variable modeling. The *circles* represent the disorders (i.e., latent variables) and the *rectangles* represent the observable core symptoms of those disorders (i.e., $X_1 - X_5$ for disorder A, and $Y_1 - Y_5$ for disorder B). In this model, comorbidity is viewed as a correlation between the latent variables, visualized by the *thick bidirectional edge* between disorders A and B.

actually *measure* a latent variable. Therefore, we consider it important to examine relationships between individual symptoms more closely.

Initiating such an endeavor is a major goal of this article. As a starting point, we propose to use the theory of complex networks. This theory has provided major contributions to current knowledge about the structure of the World Wide Web, power grids, and neural systems (e.g., see Albert & Barabási 1999; 2002; Boccaletti et al. 2006; Strogatz 2001; Wang 2002). The basic idea of the network approach is straightforward: We define and analyze relationships between symptoms, without assuming *a priori* that such relationships arise from a mental disorder as a common cause (Borsboom 2008; Van der Maas et al. 2006). Simply put, in such a network, a disorder is conceptualized as a cluster of directly related symptoms. In a fairly recent study, Kim and Ahn (2002) showed that this conceptualization comes naturally to some clinicians: depression, anorexia nervosa, antisocial personality disorder, and specific phobia were all characterized as clusters of causally related symptoms. And, adhering to such a network perspective cannot be reconciled with the psychometric properties of a latent variable model. Thus, when modeling comorbidity, we no longer assume a direct relation between two latent variables. Instead, we model comorbidity in terms of a set of direct relationships between symptoms of distinct disorders.

A network model represents symptoms as *nodes* in a graph and the relationships between them as *edges*. Figure 2 depicts an example of such a graph for two disorders: two sets of symptoms belong to two distinct mental disorders. Within each disorder, all symptoms are connected with one another, but between disorders, there are fewer (or weaker) edges between the symptoms. There are also symptoms that do not clearly belong to one or the other disorder, because they receive and send out effects to the symptoms in *both* of the disorders (i.e., overlapping symptoms). If such symptoms overlap perfectly, they can be collapsed into a single symptom, which we propose to call a *bridge symptom*. We hypothesize that in clinical practice, such bridge symptoms turn up as symptoms that are used in diagnostic schemes, such as the *DSM-IV*, for multiple disorders.

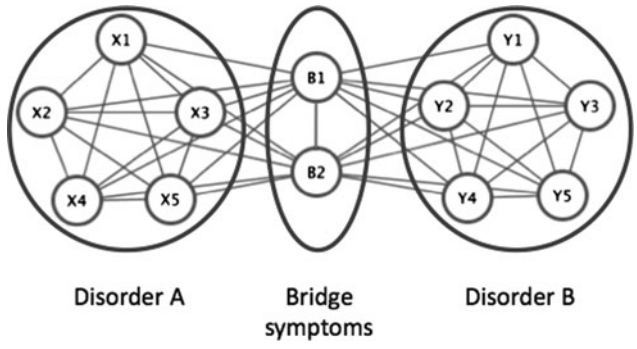

Figure 2. Comorbidity under a network approach. Disorder A consists of bidirectionally related symptoms $X_1 - X_5$, and disorder B consists of symptoms $Y_1 - Y_5$. Symptoms B_1 and B_2 are *bridge symptoms* that overlap between disorders A and B. In this model, comorbidity arises as a result of direct relations between the bridge symptoms of two disorders.

Our hypothesis regarding the crucial role of bridge symptoms in explaining comorbidity can be tested, just as a host of hypotheses can be tested with latent variable models. For binary data, a statistical parameterization of the network is a loglinear model, which is implemented in the gRbase package for R (Dethlefsen & Hojsgaard 2005). In short, with a loglinear model, one searches for the most parsimonious model – among models ranging from only main effects through models with *n*th-order interactions – that accounts for the distribution of cases in contingency tables of categorical variables (e.g., see Agresti 2002). If the main effects model should turn out to be the best model, then the MDD and GAD symptoms are statistically independent, and our hypothesized bridge model should be rejected accordingly. Thus, in gRbase, we fitted a model like the one shown in Figure 2 to the NCS-R MDD and GAD data: All symptoms of MDD/GAD, including the bridge symptoms, are connected with one another, and comorbidity arises only through connections between overlapping symptoms, on the one hand, and other symptoms of MDD/GAD, on the other hand.[2] We used the Akaike Information Criterion (AIC) to compare the fit of three models: (1) with only main effects, (2) with first-order interactions within disorders (including bridge symptoms, as in Fig. 2), and (3) with second-order interactions within disorders (including bridge symptoms). Of these three models, the best-fitting model according to the AIC is the one with first-order interactions (AIC differences are: (2) – (1) = -177.551 and (3) – (2) = 347.123). Thus, according to this analysis, the bridge model holds with all variables being statistically dependent on one another. Naturally, such a single fit is not sufficient to conclude that this model is the best choice, especially since – considering parsimony – such a low chi-square value with so many degrees of freedom cannot be interpreted in a straightforward manner. Nonetheless, this model fit shows that our hypothesis about the importance of bridge symptoms in explaining comorbidity is not a priori wrong.

The network approach is based on the hypothesis that symptoms are related *directly*. It is important to qualify this terminology to prevent misunderstandings. We intend the term "directly" to mean that the relation between symptoms is real; that is, not spurious in the sense that a latent variable model assumes it to be. This does not imply, however, there may be no intermediate processes or attributes involved. For instance, the influence of one symptom on another is likely to be mediated by, or instantiated in, a chain of processes that are not directly observable. Even the influence of the symptom "sleep disturbances" on "fatigue," mundane as it may seem, will invoke various intermediate mechanisms concerning the homeostatic processes involved in sleep regulation (Achermann 2004; Borbély & Achermann 1999; Finelli et al. 2000). Thus, within a network framework, it makes perfect sense – and is naturally necessary – to introduce non-symptom causal processes such as homeostasis that partly explain relations between symptoms. Also, such processes may involve pathways that contain some of the other symptoms in the network; for instance, a lack of sleep may lead to a loss of concentration *via* fatigue. Finally, the causal effect of a symptom may feed back into that same symptom via a loop. For instance, fatigue may lead to a lack of concentration, which may

lead to thoughts of inferiority and worry, which may in turn lead to sleepless nights, thereby reinforcing fatigue. In such a case, we have a vicious circle, or negative spiral, a well-known phenomenon to any practicing clinical psychologist. In some disorders, the existence of feedback loops is in fact considered to be a core aspect of the disorder; an example is panic disorder, in which "fear of fear" appears to play a crucial role; for instance, when the fear of having a panic attack itself contributes to the occurrence of such an attack (McNally 1994). It is therefore notable, and problematic, that in standard psychological measurement models, such phenomena cannot arise because latent variable models, being instantiations of a common cause structure, are *directed* graphs which, by definition, do not contain feedback relations[3] (Pearl 2000).

Moreover, targeting such relationships between symptoms or processes that influence such relationships is a major goal of many successful therapeutic interventions such as *cognitive therapy* (e.g., lessen the impact of cognitions on relationships between symptoms: "If I do not finish all tasks I set out to do during the day, I am a worthless person and it is better for everyone if I were gone"; see Beck et al. 1979) and *exposure therapy* (i.e., breaking the link between seeing a particular object and responding to it with fear by repeatedly exposing a patient to the feared object; see, e.g., Kamphuis & Telch 2000; Rothbaum & Schwartz 2002). It is therefore also problematic that such successful and common therapeutic interventions do not naturally arise from a latent variable perspective. This is not to say that targeting relations between symptoms is prohibited by a latent variable perspective; the more logical consequence of adopting such a perspective just seems to be to target the latent variable: eliminating the common cause will result in the disappearance of its indicators (i.e., the symptoms). In the case of major depression, for example, finding the common cause was therefore a major goal in research, with serotonin shortage being the most likely candidate. However, treatment with antidepressants that specifically target that shortage turned out to be beneficial for only some people, thereby ruling out serotonin as the common cause of depression symptoms (e.g., see Nierenberg et al. 2008). No other plausible common causes have ever been found, in our opinion due to the fact that there simply is no common cause that explains the entirety of depression symptoms.

3. An integrative method to visualize symptom associations through graphical models

Many of the efforts in complex systems theory have been aimed at providing adequate visual representations of networks, and this has yielded a number of algorithms to optimally represent networks (De Berg et al. 2008; DiBattista et al. 1994; Herman 2000), as well as freely available software to visualize them; most notable, in this respect, are the programs Cytoscape (Shannon et al. 2003 – used in constructing the graphs for this article), aiSee (http://www.aisee.com), and igraph (Csárdi & Nepusz 2006 – used in this article for the detection of community structures). We therefore propose that the study of comorbidity through network models may best start by constructing insightful visualizations.

Among a plethora of possibilities to define and visualize both nodes and edges (see, e.g., Boccaletti et al. 2006; Krichel & Bakkalbasi 2006), we propose an integrative method that, in our view, optimally visualizes key aspects of comorbidity on a symptom level. Figure 3 provides the complete key to such a *comorbidity network* for MDD and GAD, which is presented in Figure 4.[4] First, the *thickness of the edges* is determined by the co-occurrence of two symptoms: the more two symptoms co-occur, the thicker the edge between them. Second, the *color of the edges* is determined by the log odds ratio between two symptoms[5] (i.e., *strength of the association*; results available at: http://www.aojcramer.com): the higher the log odds ratio, the darker blue the edge between symptoms. (Note that other options exist to define some measure of the strength of the association between two symptoms: for instance, tetrachoric correlations.[6]) Third, the *size of the nodes* is determined by the raw frequency: the more frequent a symptom, the larger the node. Finally, the *color of the nodes* is determined by their individual *node strength* (see, e.g., Boccaletti et al. 2006; Krichel & Bakkalbasi 2006). The node strength is simply the sum of the weights of all edges that are incident in that node. In the complex networks literature, the node strength is taken to be a measure of the *centrality* of a node such that the more strength, the more central a node is in the network.

In addition, we propose the following two rules for the positioning of the nodes in a comorbidity network (see also Fig. 4): First, we propose that from left to right (i.e., the x-axis), non-overlapping symptoms of two disorders are placed on the extreme left and right while the overlapping symptoms are placed in the middle of the graph (see our Note 2). As such, one can immediately see whether comorbidity between two disorders runs mostly through the overlapping symptoms or (also) exists independently from them. Second, we propose that from top to bottom (i.e., the y-axis) the nodes are placed based on descending node strength. As such, one can immediately see which symptoms are more central in the network (i.e., top of the graph).

4. The basic structure of the depression and generalized anxiety comorbidity network

A few characteristics of the MDD and GAD comorbidity network stand out in particular (see Fig. 4[7]). First, GAD symptoms are more frequent than MDD symptoms (i.e., GAD nodes are generally larger than MDD nodes). At first sight, this may appear at odds with the higher prevalence of MDD compared to GAD that is usually reported (Carter et al. 2001; Kessler et al. 2005b). However, on a diagnosis level, only respondents who display *a certain number* of MDD or GAD symptoms with *a certain duration* qualify for a diagnosis. Additionally, because of a hierarchical exclusion rule, the GAD diagnosis will not be assigned if its symptoms occur exclusively within the course of MDD (Brown & Barlow 1992; Brown et al. 2001; Clark et al. 1995; Mineka et al. 1998; Watson 2005). Since MDD and GAD are highly comorbid (see, e.g., Brown et al. 2001; 1998; Mineka et al. 1998), such exclusion rules lower the prevalence of GAD artificially. Here, we consider data of all respondents who completed

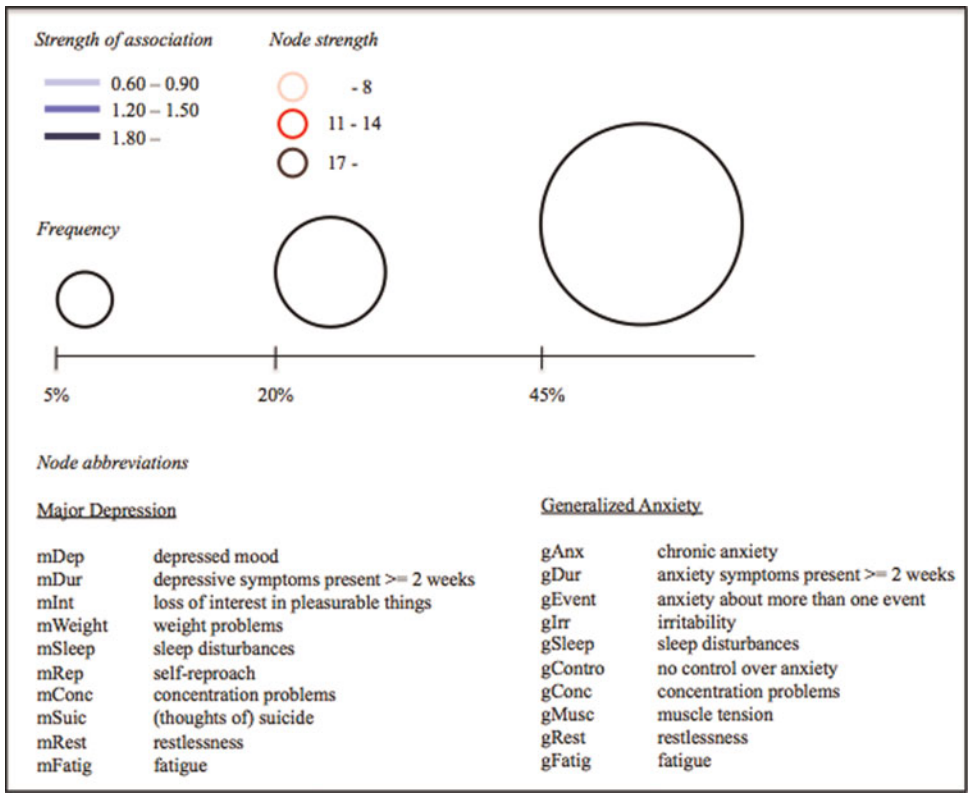

Figure 3. The key for the comorbidity networks shown in Figures 4, 5, and 6.

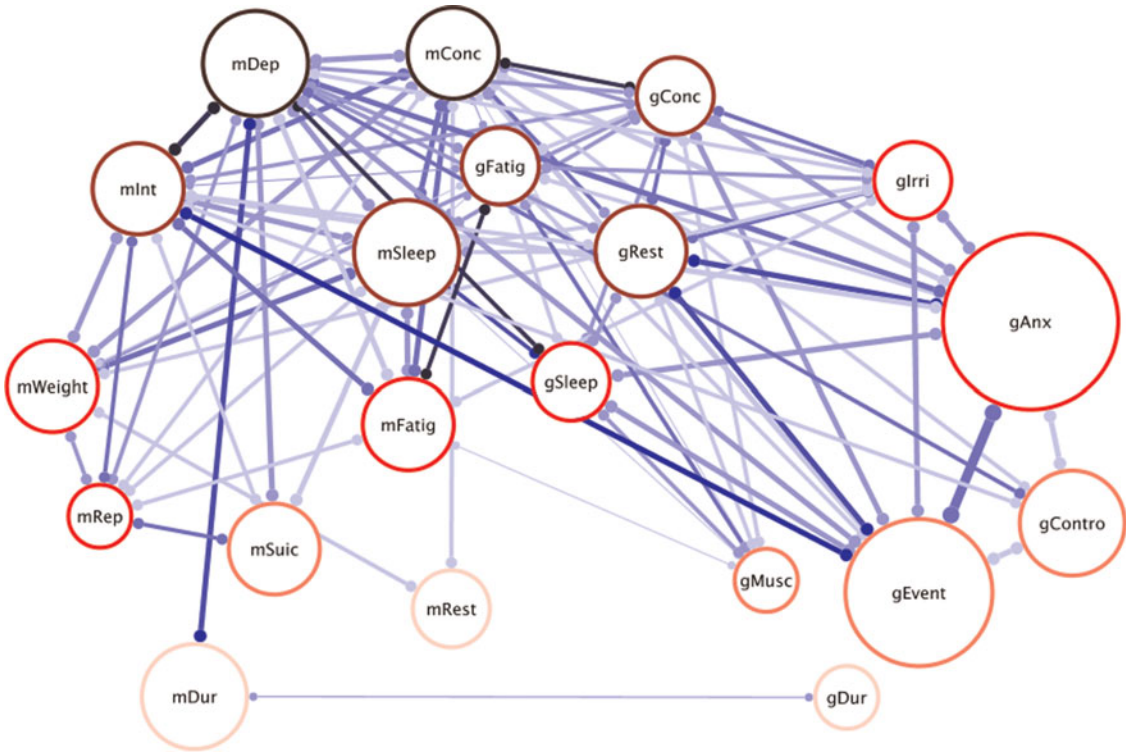

Figure 4. A comorbidity network for major depressive disorder (MDD) and general anxiety disorder (GAD). Larger nodes represent more frequent symptoms, darker circumference represents higher centrality, thicker edges represent higher frequency of co-occurrence, and darker edges represent stronger associations. Only edges with a log odds ratio higher than (+ or -)0.60 are represented. Centrally positioned nodes (*mConc*, *gConc*, *mSleep*, *gSleep*, *mFatig*, *gFatig*, *mRest*, and *gRest*) represent overlapping symptoms. Non-overlapping MDD symptoms are displayed on the *left* of the figure, and non-overlapping GAD symptoms on the *right*.

the MDD and GAD interview sections, regardless of whether or not they obtained diagnoses. As such, the network demonstrates that, when considering both subthreshold and threshold depression and generalized anxiety, symptoms of generalized anxiety are in fact more prevalent.

Second, if MDD and GAD are separate entities, we would have expected the edges to be thickest between symptoms of the same disorder (i.e., high co-occurrence). However, it is apparent that this is not the case in the network: Some of the thickest edges connect MDD with GAD symptoms; for instance, the thick edge between loss of interest (*mInt*) and reporting more than one event one worries about (*gEvent*). Also, we would have expected edges to be the darkest blue between symptoms of the same disorder (i.e., high log odds ratios), but that is also not evident when inspecting the figure. In other words, associations between symptoms of one disorder are not stronger than associations between symptoms of different disorders. These findings are in line with an earlier hypothesis that MDD and GAD are hard to distinguish on a genetic level (Mineka et al. 1998) and, as such, raise the question of whether MDD and/or GAD are truly distinct disorders. We will return to this matter in more detail in the paragraph about the non-uniformity of diagnostic criteria.

Third, duration (*mDur* and *gDur*) is hardly associated with any of the other MDD and GAD symptoms[8] (i.e., few edges are incident in those nodes). This may appear surprising since, in clinical practice, duration is key in determining the presence or absence of a mental disorder. However, if we consider medical illnesses as an analogy, the finding is potentially less surprising: Cancer will be diagnosed if a malignant tumor is present, and that diagnosis is independent of how long the tumor has been present. Thus, we could argue that, in a network approach, MDD is present whenever some symptoms are present without considering the duration of those symptoms. This is not to say that duration is not an important factor at all. Consider again medical illnesses where duration is important in determining the course of action and, subsequently, the probability of full recovery: The longer a malignant tumor has had time to grow and possibly spread, the more difficult it will be to treat it. Duration could fulfill the same role in determining the best course of action for treating mental disorders.

Finally, the strongest evidence for comorbidity stems from strong associations that involve at least one overlapping symptom (e.g., between depressed mood, *mDep*, and sleep disturbances, *gSleep*). This apparent nontrivial role of overlapping symptoms in comorbidity stands in stark contrast to earlier findings regarding MDD, GAD, and other mental disorders (e.g., see Biederman et al. 1995; Bleich et al. 1997; Clark & Watson 1991; Franklin & Zimmerman 2001; Kessler et al. 1999; Seligman & Ollendick 1998; Watson et al. 1995). We will return to this issue in more detail in the paragraph about overlapping symptoms.

It is crucial to note that the network is not necessarily complete. That is, this comorbidity network is based on the symptoms of major depression and generalized anxiety, but, naturally, it stands to reason to hypothesize the presence of factors – other nodes – that selectively influence some of the symptoms and are thus part of the network. For instance, it is well known that major life events, such as the loss of a loved one, can trigger major depression and, more specifically, there is evidence for selective influence of such personal tragedies on the more psychological symptoms of depression (e.g., depressed mood, thoughts of suicide) (David et al. 2008; Kessler 1997; Monroe et al. 2001). Also, there is evidence that traits such as neuroticism (mediated by rumination on sadness) and behavioral inhibition (i.e., shy, fearful, and withdrawn) can trigger the onset of depression and/or anxiety symptoms (e.g., see Hirshfeld et al. 1992; McNiel & Fleeson 2006; Roelofs et al. 2008a; 2008b). Because such and other more "etiological nodes" are missing from this network, they are in a sense latent. However, such latent etiological nodes do not turn the MDD and GAD comorbidity network into a latent variable model: A network with multiple latent nodes that selectively influence some of the symptom nodes is not the same as a latent variable model in which one latent factor influences all symptoms and thus entirely explains relations between symptom nodes. Moreover, an unobserved variable is indeed latent, but not every unobserved variable automatically qualifies as a latent variable in the psychometric sense in which such variables are portrayed in latent variable models commonly used in data analysis.

5. The inequality of symptoms and its consequences for diagnostic cut-offs and the definition of a mental disorder

The focus in comorbidity research is on diagnoses, which means that inferences regarding comorbidity rest on summed scores that are obtained by counting symptoms. In latent variable modeling, such an unweighted summed score is either a sufficient statistic for the latent variable (e.g., see Andersen 1973; Masters & Wright 1984) or has a monotone likelihood ratio with that latent variable (Grayson 1988). In both of these cases, inferences based on the summed symptom scores will often generalize to the latent variable. The unweighted summation of symptom scores implies that all symptoms are considered equal. Although thus formally consistent with latent variable modeling (Grayson 1988), this assumption is highly problematic and may be the origin of some significant problems in comorbidity research. In a network approach, symptoms are likely to be actually unequal in terms of their *centrality*, a property that is not reflected in any latent variable model, and this has consequences for the comparability of equal summed scores.

Suppose that Alice displays two MDD symptoms – depressed mood and loss of interest – while Bob displays two other MDD symptoms – psychomotor and weight problems. On an intuitive level, it is plausible that Alice's symptoms are more likely than Bob's to eventually result in a full-fledged depression. In other words, some symptoms appear to be more *central* features of depression than others. The comorbidity network sustains this intuition. When considering the node strengths in Figure 4 (i.e., colors of the nodes), one immediately sees that, indeed, depressed mood (*mDep*) and loss of interest (*mInt*) are far more central in the network than are psychomotor (*mRest*) and weight problems (*mWeight*). In other words, the same summed score of Alice and Bob

may not adequately capture that the symptoms of Alice result in a higher probability of developing other MDD symptoms – and thus augment the probability of eventually developing depression – compared to Bob's symptoms. Hence, summed scores appear to be *incomparable*, at least with respect to elucidating which people with subthreshold depression problems are at more risk of developing MDD. Naturally, such symptom inequalities are widely recognized among psychiatrists and clinical psychologists, and they do occasionally appear in *DSM-IV* (e.g., depressed mood and loss of interest as central features of major depression); the problem is, however, that the models that underlie current comorbidity research do not naturally allow for them.

If our line of reasoning is correct, and there is no latent variable that screens off correlations between symptoms (*a latent variable model renders all symptoms equally central and thus exchangeable*[9]), then the inequality of symptoms in terms of their centrality also renders diagnostic cut-offs open to debate. We are certainly not the first ones to point out that diagnostic cut-offs appear to be arbitrary (e.g., see Gotlib et al. 1995; Lilienfeld & Marino 1999; Maier et al. 1997; Solomon et al. 2001). For instance, there are individuals who do not meet diagnostic criteria for MDD yet appear to be psychosocially as dysfunctional as individuals who are diagnosed with MDD; that is, the consequences of subthreshold MDD problems may not always be distinguishable from those of diagnosed MDD. With the network approach, we offer a potential explanation of such findings. Suppose that Alice displays four MDD symptoms and Bob five. The diagnostic cut-off of criterion B for MDD is five, so Alice would not be diagnosed with MDD while Bob would. So far so good, but now suppose that Alice's symptoms are all highly central in the MDD network while Bob's are more peripheral. Is it, in such a scenario, plausible to conclude that Alice is not depressed and Bob is? In other words, based on diagnostic cut-offs, we may fail to disentangle symptom-specific effects, because such cut-offs do not take into account the centrality of symptoms.

This brings us to another important point: namely, the definition of a mental disorder, generally conceptualized as "Disorder A is X or more symptoms out of Y possible symptoms." According to a latent variable perspective, it is not only perfectly defensible to entertain such a definition, but the definition is the same for every single individual; that is why Alice is not depressed and Bob is. However, if symptoms are not exchangeable in terms of their centrality, as we think is plausible, one cannot help but question such a definition of a mental disorder. In other words, if diagnostic cut-offs alone are no longer the demarcation line above which someone suffers from a particular mental disorder, then how do we define a mental disorder?

From a network perspective, there are several possibilities to define what constitutes a mental disorder. As a starting point, we propose to define a disorder as a cluster, a set of nodes (symptoms) that are strongly connected. Now, from a graph theoretic perspective, there are multiple ways to define in what sense a set of nodes is strongly connected (see, e.g., Hubert 1974). First, let us call the giant network consisting of all symptoms of all mental disorders (i.e., the entire *symptom space*) as defined in the *DSM-IV*, graph G. Then a subgraph H (for instance, consisting of all MDD symptoms) is a cluster of G if and only if the minimum node strength of H is larger than the minimum node strength of H + {n}, with n any other node adjacent to H (*Definition 1*). It is also possible to define a subgraph H as a cluster of G if and only if the minimum of the average distance between all nodes in H is strictly smaller than that of H + {n} for any node n in G (i.e., closeness; see, e.g., Boccaletti et al. 2006) (*Definition 2*). Other definitions are possible, and it is – in our opinion – up to future debate and research to determine which is the most sensible one. Second, now that we have hypothetically defined the cluster of all possible symptoms of a disorder, we need to determine when such a cluster is disordered. One plausible candidate is a modified version of the diagnostic cut-off; for example, in the case of MDD, at least three *of the most central* symptoms in the entire MDD cluster (with "central" either defined as the nodes with the largest node strengths, or as the smallest average distance within the cluster). In contrast to a latent variable perspective, both definitions acknowledge the centrality differences of symptoms but, at the same time, accept the inevitable fact that some form of a diagnostic cut-off is needed to disentangle people with and without a disorder.

A related point concerns the *external* effects of different symptoms. One readily imagines extending a network with variables that are not part of the disorder itself, but constitute nontrivial consequences of many mental disorders (e.g., losing one's job, lowered educational achievement, or suicide attempts). It is interesting to note that, under the assumption of a latent variable model, it is the latent variable that has a direct relationship with external effects, and not the symptoms. Due to the absence of a direct relationship between a symptom and an external effect, this means that a symptom can never be statistically independent of such an external effect, given another symptom. Thus, for instance, a suicide attempt by someone with thoughts of suicide and concentration problems (and three other symptoms resulting in a diagnosis of major depression) is entirely attributable to the overarching latent depression and, given the thoughts of suicide, the concentration problems are thus still associated with the suicide attempt. In our view, it would be more logical to hypothesize a direct relationship between thoughts of suicide and a suicide attempt and a weaker or perhaps even nonexistent relationship between concentration problems and a suicide attempt. In the same vein, it appears to make sense to envision a stronger relationship between concentration problems and losing one's job than between losing weight and losing one's job. This differential impact of symptoms on external effects is not possible in a latent variable model, whereas it is very easily envisioned within a network perspective.

Centrality differences between symptoms imply that there probably will be pathways to comorbidity that are more likely (i.e., strong connections between symptoms that are central in a network) than others. Figure 4 confirms this idea: One likely pathway to comorbidity connects depressed mood (*mDep*) with sleep problems (*gSleep*) and anxiety (*gAnx*). Less likely pathways involve psychomotor problems (*mRest*) because this symptom has such weak associations with the other symptoms in the network. Naturally, inspecting a graph is not enough to draw any solid conclusions on the pathways to

comorbidity between MDD and GAD, but we do think it is evident that the network approach could contribute to finding answers to this question, if only because the visual representation of a network immediately leads to a host of interesting hypotheses.

6. Non-uniformity of mental disorders

Quite a few scholars are *essentialists* in describing the relationship between the two main diagnostic categories "disorder" and "no disorder" that are based on diagnostic criteria and the real world (e.g., see Haslam 2000; Haslam & Ernst 2002; Lilienfeld & Marino 1999): The diagnostic criteria we use result in a distinction between disordered and non-disordered people that also exists in the real world. Seductive as this line of reasoning may seem, in order for it to be true, two conditions must be satisfied. First, a mental disorder must have *defining features* such that everyone, based on those defining features, could be assigned to the "disorder" category (i.e., defining features are present) or the "no disorder" category (i.e., defining features are absent) provided that these features were known with certainty. Second, as a result, all members of the same category must essentially be the same with respect to those defining features (i.e., *uniformity*). Down's syndrome is a good example of a medical disorder that satisfies those two conditions: The syndrome has one defining feature, the presence of all or part of an extra 21st chromosome, and everyone with Down's syndrome possesses that defining feature while everyone without Down's syndrome does not possess it.

This line of reasoning is unlikely to hold for mental disorders. First, quite a few mental disorders do not have defining features, at least not in an essentialist sense. For example, besides depressed mood or loss of interest, which must always be present for a person to be diagnosed as having MDD, *any* constellation of five symptoms (i.e., features) will suffice to fulfill criterion B for MDD. When any such constellation of symptoms is present for at least two weeks in an individual, then that individual will be assigned to the "MDD" category, otherwise to the "no MDD" category. This renders the core features of depression non-defining because, for instance, someone with the feature "depressed mood" could end up in the "MDD" category – because he or she suffers from five or more symptoms for more than two weeks – as well as the "no MDD" category if he or she suffers from less than five symptoms or the symptoms are present for less than two weeks. Second, as a result of the lack of truly defining features, the "basket" with depressed people does not contain uniform members: Pete is depressed because he suffers from sleep disturbances, fatigue, concentration problems, depressed mood, and psychomotor problems, while Anne is depressed because she suffers from depressed mood, loss of interest, self-reproach, weight problems, and thoughts of suicide.

As such, one must wonder whether the distinction between "disorder" and "no disorder," as we have defined it in our diagnostic criteria, actually exists in the real world. Latent variable modeling schemes posit the existence of such a categorical system (in a latent class model) or a continuous one (in a factor or item response theory [IRT] model) as a hypothesis. Hence, such models are consistent with the hypothesis that we may one day find out "what depression really is"; that is, latent variables may "become" observed through a refinement of the conceptual and measurement apparatus used to study them (e.g., Bollen 2002; Borsboom 2008). However, in the absence of such refinements, the acceptance of the latent variable hypothesis depends at least partly on its explanatory virtues (Haig 2005), and in the context of comorbidity research these explanatory virtues are, at present, quite limited. That is, apart from the fact that such a model would explain why correlations between symptoms are positive and that it more or less fits the observed frequency of symptom patterns, there is little that speaks in its favor.

When studying comorbidity based on diagnoses, this inevitably leads to the question of what we actually observe when two disorders covary: genuine covariation between two real disorders, or covariation between certain constellations of symptoms we have designated to be disorders, but that are in fact not indicators of the same latent variable? This issue, of course, has generated a heated debate through the history of psychiatry and clinical psychology (Haslam 2000; Haslam & Ernst 2002; Jablensky 2007; Kendell 1975; Klein 1978; Krueger & Markon 2006b; Lilienfeld & Marino 1999; Richters & Hinshaw 1999; Spitzer 1973; 1999; Spitzer & Endicott 1978; Wakefield 1992; 1999a; 1999b; Zachar 2000; Zachar & Kendler 2007). The network approach could contribute to finding an answer to this question in two ways: first, by utilizing techniques to find what is called a *community structure*, and second, by reconceptualizing the question itself, and thereby the range of possible answers.

The community structure of a network refers to the existence of at least two clusters of nodes, such that the nodes within a cluster are highly connected with one another, but only modestly or sparsely with the nodes within another cluster (see Newman 2006; Newman & Girvan 2004). We analyzed the community structure of the MDD and GAD comorbidity network twice with a spin-glass algorithm (for technical details, see Reichardt & Bornholdt 2006): one time with co-occurrence between symptoms as edge weights and one time with the log odds ratios between symptoms as edge weights. The results are in line with the notion that there is no essential distinction between MDD and GAD, as has also been found in behavioral genetics and diagnostics research (Mineka et al. 1998; Wadsworth et al. 2001): Our network reveals no community structure whatsoever, regardless of which edge weights were used; that is, the comorbidity network did not differ from a random network in terms of connectivity between nodes. These results suggest that MDD and GAD may not be separate entities. Naturally, this conclusion may be different for other mental disorders.

We are by no means pioneers when claiming that boundaries between diagnostic categories are *fuzzy*, for this phenomenon was noticed quite some time ago (e.g., see Kendell 1975; Klein 1978; Spitzer 1973; Spitzer & Endicott 1978). However, earlier ponderings have not included an account of *why* the boundaries are fuzzy and, in our view, a network approach offers such an explanation. If we are indeed correct to assume that a mental disorder is best conceptualized as a network of symptoms and – consequently – comorbidity is best viewed as a network of symptoms of two disorders, then boundaries

are fuzzy *because they simply do not exist*. And the reason that they do not exist lies in the fact that the networks are not isolated from each other. The very fact that there are bridge symptoms precludes such a situation from occurring. As a result, we can draw the line between disorders A and B everywhere in the network. For instance, we could draw a boundary between MDD and GAD such that MDD contains only non-overlapping MDD symptoms while GAD contains its own symptoms and the overlapping MDD symptoms. Or, we could draw a boundary such that MDD only contains non-overlapping MDD symptoms and GAD only its non-overlapping symptoms. In other words, from a network perspective, the *DSM-IV*–defined boundary between MDD and GAD is no more defensible than any other boundary.

The network perspective offers an intermediate position between essentialism and conventionalism regarding mental disorders and the comorbidity that exists between them. On the one hand, there is a sense in which the delineations of mental disorders are arbitrary (there is no preferred line that separates the relevant networks). One the other hand, since realizations of common causes for symptom clusters cannot be detected, the actual phenomenon of comorbidity is not a matter of convention, since it depends on causal patterns that exist in the real world, independent of the researcher who studies them. Although mental disorders can be defined as a network in various ways, which may reflect mainly pragmatic concerns, comorbidity will remain regardless of how one draws the lines. In this sense, comorbidity may be more real than the mental disorders on which it is defined.

This is consistent with, and may actually offer an explanation of, results typically found in quantitative behavior genetics. Through twin studies and related methodologies, it has been established that a considerable portion of the individual differences in anxiety and depression, as well as many other psychological variables, is determined by genetic factors (Boomsma et al. 2002; Kendler et al. 2001; McGue & Christensen 2003). Much research has focused on determining the genes responsible for this fact, but so far these efforts have been moderately successful at best, with the typical result being that individual polymorphisms do not account for more than a minor portion of the phenotypic variance (e.g., 1% or 2% at best). Thus, such phenotypes are highly polygenetic. The network account explains this naturally: It is likely that the strength of connections between symptoms (e.g., the relation between lack of sleep and irritability) differs over individuals, and it is also likely that these individual differences are at least partly under genetic control. However, a network of k nodes consists of k^2-k relations between distinct nodes (380 possible relations for the network in Fig. 4), and it is rather unlikely that the strength of *each* of these relations stands under control of the *same* genes. Thus, the network approach is not only consistent with the fact that most psychological phenotypes are polygenic, but may actually offer an explanation of that fact. In addition, the approach suggests that gene-hunting efforts may be better served by relating polymorphisms to the *relations* between symptoms, rather than to *composites* of symptoms such as total scores on questionnaires.

The possibility of individual differences in a network structure raises the question of whether a uniform definition of comorbidity exists. For example, is there a particular *sequence* in which two comorbid disorders arise that holds for every single individual? At first sight, this appears to be unlikely. However, even though there may be individual differences in qualitative structure and quantitative characteristics of networks, statistical considerations regarding the average strength of connections may suggest pathways that are more or less prevalent in the population.

For instance, in contrast to Moffitt et al. (2007), who found that MDD and GAD were equally likely to be the first in the comorbidity sequence, the MDD and GAD comorbidity network (see Fig. 4) does suggest the existence of a general pathway: namely, from MDD to GAD. First, because the non-overlapping MDD symptoms are not highly associated with one another, it does not appear to be very likely that someone with a few non-overlapping MDD symptoms will progress to other non-overlapping MDD symptoms. Second, a pathway from non-overlapping to overlapping MDD symptoms to GAD symptoms could be more likely because of stronger associations between those types of symptoms. The converse scenario – that is, from GAD to MDD – appears to be less likely in this particular network. In general, associations between non-overlapping GAD symptoms are relatively strong, at least stronger than between the symptoms of MDD, and, most importantly, more or less as strong as associations between non-overlapping and overlapping GAD symptoms. As such, when in the GAD network, to progress quickly from a few non-overlapping GAD symptoms to overlapping GAD symptoms and from there to MDD symptoms, does not appear to be more likely. Instead, it appears to be equally likely that someone stays in the GAD network without progressing to MDD symptoms. Given the structure of this particular MDD–GAD network, we therefore hypothesize that Neale and Kendler (1995) are correct in concluding that the most likely pathway could indeed be from MDD to GAD.

Naturally, further research involving the time course and etiology of mental disorders is required to test this hypothesis. It should be noted, however, that the hypothesis follows naturally from a (tentative) causal interpretation of the network: the stronger the association between symptoms, the more likely that one symptom will lead to another. Furthermore, a causal explanation of a network suggests that some symptoms within a disorder put one at greater risk for comorbidity than do others. To the contrary, one does not get these implications from either unidimensional or two-dimensional latent variable models that assume exchangeable symptoms, save for measurement precision (see Bollen [1989] for a good explication of this point). Thus, studying the etiology of symptoms may offer interesting insights with respect to the question of whether symptom development is best conceptualized in terms of a latent variable model, or in terms of a network perspective. We therefore consider the direction of research efforts toward the study of temporal dynamics of symptoms to be essential.

7. Symptom overlap between disorders

A final problem with current comorbidity research has to do with the fact that many disorders share a number of symptoms: sleep disturbances, fatigue, restlessness, and

concentration problems in the case of MDD and GAD (American Psychiatric Association 1994). The obvious problem of such symptom overlap is that it raises doubt as to whether comorbidity is a real phenomenon: If we would remove overlapping symptoms from our diagnostic system, would comorbidity estimates look more or less the same, or is it that comorbidity is just that, symptom overlap? The latter does not appear to be true. Numerous researchers have approached this problem via different angles and with respect to different disorders, and the majority have reached the same conclusion: Yes, there is considerable symptom overlap between some disorders, but it seems highly unlikely that this overlap explains most systematic covariation between those disorders (e.g., see Biederman et al. 1995; Bleich et al. 1997; Franklin & Zimmerman 2001; Kessler et al. 1999; Seligman & Ollendick 1998).

However, there are reasons to argue that some of the methodological approaches to study the effects of symptom overlap are problematic, rendering the conclusions based on such approaches open to debate. For instance, Bleich et al. (1997) removed symptoms that overlapped between post-traumatic stress disorder (PTSD) and MDD and re-diagnosed Israeli combat veterans who were already diagnosed with PTSD and/or MDD. The results showed that, after the removal of the overlapping symptoms, 98% (95%) of the veterans with lifetime (current) MDD were re-diagnosed with MDD, whereas 70% (55%) of the veterans with lifetime (current) PTSD were re-diagnosed with PTSD. Besides the fact that the re-diagnosis percentage of both lifetime and current PTSD is somewhat low, the problem with this approach is that re-diagnosing someone with MDD without overlapping symptoms does not prove that symptom overlap does not play a role in the *etiology* of comorbidity between MDD and another disorder.

Suppose that someone endorses eight MDD symptoms, three of which overlap with GAD. Two problems arise here. First, the effect of removing the overlapping symptoms depends on the diagnostic cut-off: This person will be re-diagnosed with a cut-off of five while with a cut-off of four, there will be no re-diagnosis. Hence, conclusions about the effects of removing overlapping symptoms depend entirely on diagnostic cut-offs that, as we noted earlier, are at least partially arbitrary. Second, and more important, it is impossible to exclude that a re-diagnosis actually signals the major impact of overlapping symptoms in explaining the etiology of comorbidity: What if overlapping symptoms are relay stations that trigger the onset of symptoms in the entire network, resulting in a comorbid diagnosis? As such, a subsequent re-diagnosis does not have to signal the relative unimportance of overlapping symptoms. To the contrary, it could be justifiably taken to mean that overlapping symptoms have a seminal role. They cause comorbidity with such a profound effect on the network that removing them does not affect the initial diagnosis: the damage has already been done.

This is not to say we think that the removal of overlapping symptoms to study its effects is a bad idea per se. We think it is a useful starting point, but (a) the effects of removing overlapping symptoms are perhaps better studied on a symptom level instead of on a diagnosis level, and (b) the matter should be investigated further; for instance, by not removing overlapping symptoms but by separately analyzing a subgroup: people who display one or more overlapping symptom pairs. Thus, we first investigated the impact of removing the six symptoms that overlap between MDD and GAD, as well as their associations with all other symptoms from the comorbidity network in Figure 4, resulting in Figure 5 (see Fig. 3 for the key). This figure confirms our initial suspicions: without the overlapping symptoms, not much comorbidity

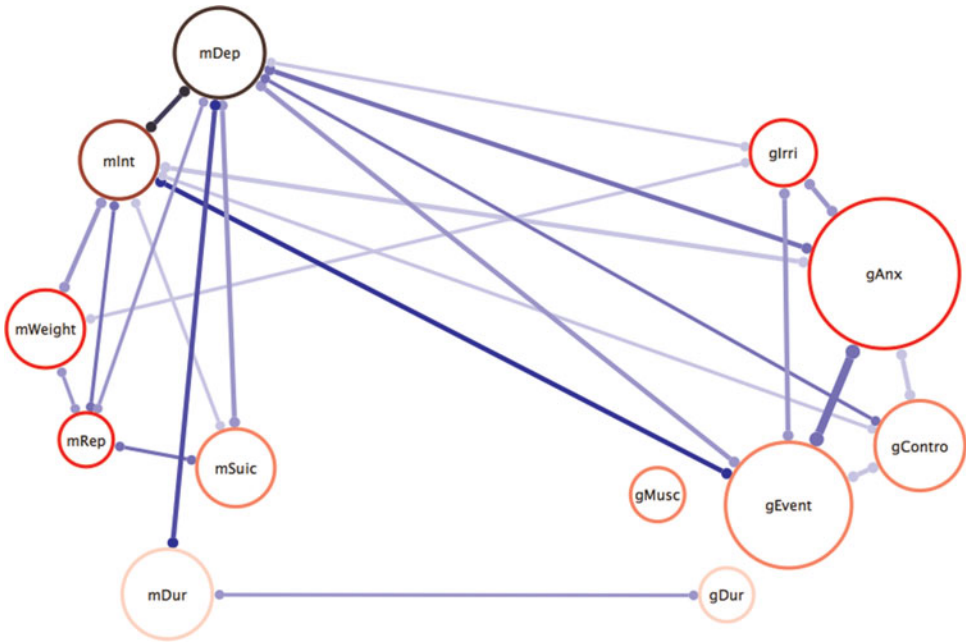

Figure 5. The comorbidity network for major depressive disorder (MDD) and general anxiety disorder (GAD) after removal of the overlapping symptoms and their bivariate associations with the other symptoms. This network is based on exactly the same four characteristics as the full network in Figure 4.

seems to remain. In fact, only depressed mood (*mDep*) and loss of interest (*mInt*) have some relatively strong connections with GAD symptoms such as anxiety (*gAnx*), loss of control (*gContro*), and number of events that cause worry (*gEvent*).

Next, we performed the subgroup analysis: We thus computed log odds ratios, co-occurrences, frequencies, and node strengths for only those respondents who displayed at least one *pair* of overlapping symptoms (e.g., both MDD and GAD concentration problems; $N = 1{,}059$).[10] Figure 6 presents their comorbidity network without the overlapping symptoms (see Fig. 3 for the key). This figure leaves no room for doubt about the importance of overlapping symptoms: All symptoms are more frequent and co-occur more frequently, and having one symptom increases the odds of having another one substantially (and thus the node strength) compared to the comorbidity network in Figure 5. Taking all results together, it is likely that overlapping symptoms play a more important role in explaining comorbidity than was originally thought.

8. Conclusions and future directions

In this article, we have introduced a radically different conceptualization of mental disorders and their symptoms: namely, the *network approach*. Under the assumption of such an approach, a mental disorder is a network of symptoms that stand in direct, possibly causal, relations to one another. Comorbidity between mental disorders is then conceptualized as direct relations between symptoms of multiple disorders. We have argued that such an approach bears a closer resemblance to the reality of mental disorders and comorbidity between them, as it allows for (1) multiple etiological processes that interact in causing symptoms, (2) interindividual differences in the manner in which a constellation of symptoms is contracted, (3) direct relations between overlapping symptoms, and (4) inequality of symptoms. Also, we have proposed an integrative method, based on bivariate associations, to visualize comorbidity networks.

Based on such an empirical network for major depression and generalized anxiety, we showed that a network approach results in a host of realistic and testable hypotheses that are not naturally accommodated by latent variable models. First, it is likely that there exist pathways to comorbidity through the symptom space that are more likely than others (e.g., via core psychological symptoms such as depressed mood and loss of interest). Second, it is plausible that those pathways generally follow the same direction (e.g., we found that comorbidity from major depression to generalized anxiety appeared to be more likely than the other way around). Finally, overlapping symptoms play a more than trivial role in explaining the roots of comorbidity (i.e., we showed that symptoms of major depression and generalized anxiety were more strongly connected in people who displayed at least one pair of overlapping symptoms).

The present work bears interesting relations to that of Van der Maas et al. (2006), who showed that the positive manifold of correlations between various IQ tasks – often thought to result from a single latent variable, general intelligence – may result from a dynamical system in which a network of bidirectionally related cognitive processes beneficially interact with one another during development (i.e., the *mutualism model*). The mutualism model serves as an excellent starting point for developing a unified theory for mental disorder networks because of their similarities. For instance, the mutualism

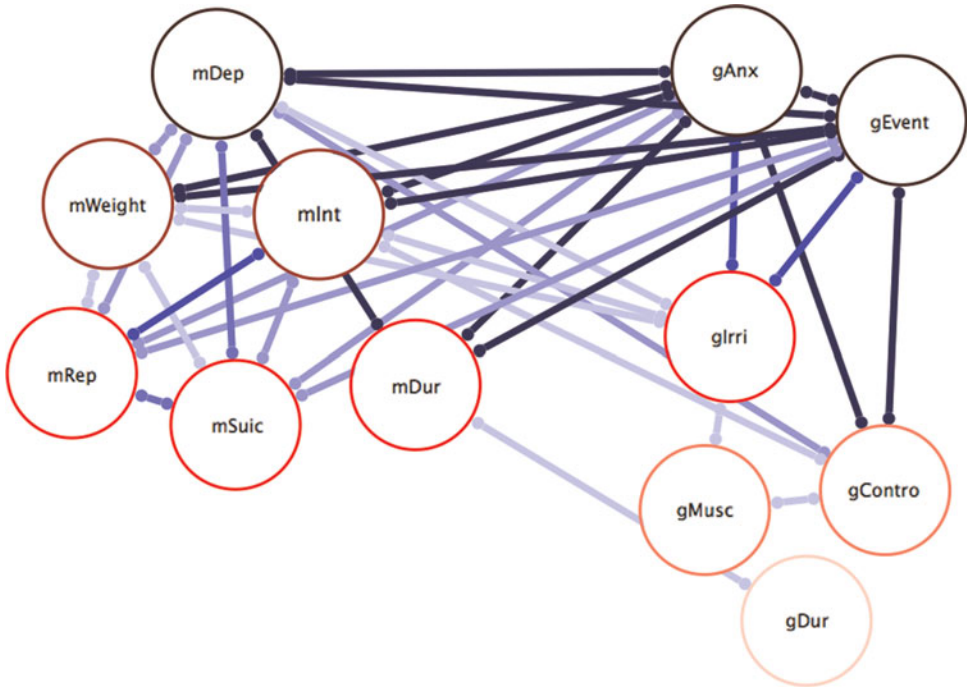

Figure 6. A comorbidity network for major depressive disorder (MDD) and general anxiety disorder (GAD) for those respondents ($N = 1{,}059$) who displayed at least one pair of overlapping symptoms. This network is based on exactly the same four characteristics as the network in Figure 5.

model is a *dynamical system* (Alligood et al. 1997) (for examples of dynamical systems in other areas of psychology, see Cervone 2004; Shoda et al. 2002; Van Geert 1998). Such a system consists of a set of possible states with a rule that determines the present state in terms of past states. At any point in time, dynamical systems are in a particular state and that state can be represented as a point in *state space*. If a dynamical system evolves long enough, then it will encounter one or more *attractors* in state space: regions in state space that the system will move towards and enter. In state spaces with more than one attractor, some systems tend to move towards one attractor and remain there in a stable state (i.e., *monostable systems*; see, e.g., Pisarchik & Goswami 2000).

The mutualism model is an example of such a monostable system. Like the mutualism model, mental disorders are also dynamical systems that evolve over time. However, unlike the mutualism model, mental disorder networks are probably minimally *bistable systems* with a "disorder" attractor state and a "no disorder" attractor state between which the system oscillates. For example, in a substantial number of people who suffer from major depression, it is a well-established fact that depressive symptoms come (i.e., the system moves towards a "depressed" attractor state), and go (i.e., the system moves towards a "not depressed" attractor state), either through therapeutic intervention or spontaneous remission (e.g., see Posternak & Miller 2001). Some mental disorders may be *multistable systems* with the system oscillating between more than two attractor states. It is possible that bipolar II disorder is a system that oscillates between hypomania, major depressive episodes, and, under the influence of therapeutic interventions, remission states. Dynamical systems theory can be used to predict the *trajectory* of a system in the state space; that is, future states of the system can be predicted from earlier states, a technique that is, for instance, widely employed in weather forecasting (e.g., see Palmer 2001). Analogously, such techniques could in the future be used to predict trajectories of a variety of mental disorders, given the initial state of a network for an individual. If there are individual differences in the precise structure of networks, this may require person-specific network structures to be determined for each individual separately, as is, for instance, possible through the analysis of intra-individual time series (Hamaker et al. 2007; Molenaar 2004).

The trajectory of any mental disorder as dynamical system cannot be adequately predicted without taking external variables into account. One important feature of many mental disorders is that all or most symptoms are positively correlated. As such, when modeling the reality of mental disorders from a dynamical systems perspective, if people enter the network by displaying one symptom, this symptom will quickly turn other symptoms "on." As a result, the trajectory of such a system will be predictable and unrealistic: everyone will "contract" the mental disorder. In reality, there are many external variables that mitigate relationships between symptoms: good news that prevents someone progressing from depressed mood to thoughts of suicide, homeostasis due to which someone with sleep difficulties will not stay fatigued indefinitely, and so on. Such external variables thus play a critical role in determining toward which attractor state the system moves, and, as such, must be included in mental disorder systems.

Also, we should take into account the possibility that the entire symptom space network displays characteristics of a *small world* (e.g., see Barrat & Weigt 2000; Rubinov et al. 2009; Watts & Strogatz 1998). A small-world network is a highly clustered network with relatively short characteristic path lengths (i.e., it takes relatively few steps to "travel" from one node in the network to another). Networks with such properties are frequently found, ranging from the power grid of the western United States through the neural network of the worm *Caenorhabditis elegans*. If a general mental disorder system would indeed also display small-world features, it potentially offers a powerful explanation of the generally high comorbidity between mental disorders (i.e., short characteristic path lengths). Also, it would reconfirm the existence of distinct symptom clusters that represent distinct mental disorders (i.e., high clustering).

Finally, any adequate general network model for mental disorders must encompass the fact that mental disorders as systems are essentially *complex* (e.g., see Cilliers 1998): Because of the interplay between the individual components (i.e., symptoms) of the system and the interaction between the system and its environment, the system/disorder as a whole cannot be fully understood by analyzing its individual components. Also, these interactions change over time, and this can result in *emerging properties*, properties of the system that are not evident from inspecting the individual components. In complexity research, rapid advances are made with respect to modeling emerging properties in complex systems, and the network approach for mental disorders could benefit from those advances (see, e.g., Paik & Kumar 2008; Solé et al. 2000). An important additional question is how dynamical properties of complex systems relate statistically and conceptually to interindividual differences as commonly analyzed with latent variable models (Molenaar 2003).

As such, multiple insights from various research disciplines may be further developed and combined into a general psychometric theory of mental disorders as networks. Such a theory should, in our view, address the dynamical nature of causal systems (i.e., model that tracks the development of a mental disorder network over time), allow for representing the influence of external variables (e.g., treatment that potentially turns symptoms "off"), and allow for an adequate conceptualization of causal relations between symptoms. Advances in the areas of complexity and dynamical systems may be of considerable help in constructing such a theory. Also, given the relevance of results from various disciplines (e.g., mathematics, physics, and computer science), the construction of a viable psychometric theory based on these ideas is likely to involve the integration of theory and methods from different fields, and we therefore hope to attract the attention of scholars from a wide variety of disciplines. The need for a general theory of this type is, we think, evident: We have been looking at mental disorders through the wrong psychometric glasses, and it is high time for us to craft new ones.

ACKNOWLEDGMENT

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NOTES

1. The National Comorbidity Survey Replication (NCS-R) is a nationally representative household survey of English speakers 18 years and older in the United States (see Kessler et al. 2004). The NCS-R survey schedule is the version of the World Health Organization (WHO) Composite International Diagnostic Interview that is developed for the WHO World Mental Health Survey Initiative (WMH-CIDI; Kessler & Ustun 2004). The interviews were conducted between February 2001 and April 2003. A total of 9,282 respondents participated in Part 1 of the interview (core diagnostic assessment) that we used for this article. The symptoms that participants reported within one disorder all occurred within the same time frame.

2. We did not collapse the six symptoms that overlap between MDD and GAD into three bridging symptoms because the log odds ratios between each pair of overlapping symptoms were not high enough to warrant such a collapse. A probable explanation for this is that some people, for instance, did report concentration problems in the depression section, but were unable to report those same problems in the generalized anxiety section because that section was skipped (e.g., because the respondent did not experience chronic anxiety).

3. It is prudent to note that feedback loops can create considerable methodological difficulties in model fitting, because they lead to models that cannot be recursively estimated. However, given our present state of ignorance concerning the nature of comorbidity, we think it is more useful to construct a theoretical representation that is likely to be faithful to reality, than it is to construct a model based on a list of desirable computational properties.

4. This network is based on the NCS-R questionnaire that mostly contains dichotomous items. However, some of the items were not (e.g., "How many pounds have you gained?"), and we dichotomized those according to the *DSM-IV* diagnostic algorithms. Details of the dichotomization process are provided at: http://www.aojcramer.com.

5. The *odds ratio* is the ratio of the odds of an event (e.g., suffering from loss of interest) occurring in one group (e.g., people who suffer from depressed mood) to the odds of that event occurring in another group (e.g., people not suffering from depressed mood). For cell counts in a 2x2 contingency table, the sample odds ratio equals $n_{11}n_{22}/n_{12}n_{21}$ (see Agresti 2002). Since the odds ratio scales between zero and infinity, with a value of 1 signifying the absence of association, the odds ratio is not optimal for visualization in our network; therefore, we used the natural logarithm of the odds ratio. A log odds ratio of 0 (i.e., an odds ratio of 1) indicates that the event is equally likely in both groups. Please note that a high co-occurrence ($= n_{11}$) does not necessarily imply a high odds ratio. For example, (1) a high co-occurrence ($n_{11} = 500$), (2) almost no people who do not have both symptoms ($n_{22} = 3$), and (3) thus, relatively many people who have one or the other symptom ($n_{12} = 15$ and $n_{21} = 100$) yields an odds ratio of 1 (500*3/100*15), signaling no association between those symptoms. Thus, co-occurrences and odds ratios show different aspects of a data set.

6. In fact, we also computed tetrachoric correlations for the MDD and GAD symptoms with a full information maximum likelihood approach through which we dealt with the missing values that were Missing At Random (MAR). We found that the ordering of the symptoms in terms of their node strength was nearly the same as with log odds ratios.

7. We have checked the stability of the results depicted in this figure by randomly splitting the sample in two and running all analyses for both groups separately. Those separate analyses revealed the same results and, therefore, we consider the components of Figure 4 to be stable.

8. The fact that duration is weakly associated with the other MDD and GAD symptoms cannot be explained by a skip structure that only allowed respondents to progress to the other symptoms' section if they fulfilled the duration criteria for depressed mood/loss of interest (MDD: more than 2 weeks) and chronic anxiety (GAD: more than 6 months): respondents with depressed mood/loss of interest for at least 3 days for more than 1 hour per day (MDD) as well as respondents with chronic anxiety for at least 1 month were allowed into the sections about the other symptoms.

9. It is important to note here that within a latent variable framework, factor loadings cannot be measures of symptom centrality as we view the concept, since those loadings are simply reliability estimates: the higher the factor loading, the more reliably an indicator "represents" the common cause.

10. The contingency tables, as well as the computational script (made in R), are available at: http://www.aojcramer.com. We have checked the stability of the results depicted in Figure 6 by randomly splitting the sample in two and have run all analyses for both groups separately. Those separate analyses revealed the same results, and therefore, we consider the components of Figure 6 to be stable.

Open Peer Commentary

Latent variables and the network perspective

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Abstract: We discuss the latent variables construct, particularly in regard to the following: that latent variables are considered as the sole explanatory factor of a disorder; that pragmatic concerns are ignored; and that the relationship of these variables to biological markers is not addressed. Further, we comment on the relationship between bridge symptoms and causality, and discuss the proposal in relationship to other constructs (endophenotypes, connectionist-inspired networks).

Since the early stages of the discipline of psychiatry, the construct of psychiatric semiology and nosography has been indissociable from the etiological conceptualization of observed phenomena. Nevertheless, it is widely admitted that psychiatric disorders are multifactorial and etiologically complex, and explanatory models should refer mostly to *explanatory pluralism* rather than to *biological reductionism*. Our knowledge about psychiatric disorders remains incomplete, and we can only hope to get "small explanations, from a variety of explanatory perspectives, each addressing part of the complex etiological process leading to disorder," and try to understand "how these many different small explanations all fit together," etiological pathways being considered "complex and interacting more like networks than individual pathways" (Kendler 2005, p. 435). Our current categorical classifications of mental disorders in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (*DSM-IV*; American Psychological Association 1994) and in the World Health Organization's International Statistical Classification of Diseases, 10th revision (*ICD-10*) have been conceptualized on assumptions of more global and simple hypothetical explanations.

In that context, the clinical assessment of psychiatric conditions has been addressed in reference to the "latent trait hypothesis," which considers each observed symptom or cluster of symptoms to be related to a specific latent cause.

Any attempt to go beyond the usual categorical construct of current mental disorders classifications could constitute a valuable epistemological contribution in view of the upcoming new version of mental disorders classifications (*DSM-V*), as it takes an important step toward a less categorical, and rather dimensional conception of mental disorders. We have the following specific comments to make on Cramer et al.'s discussion of latent variables in the target article.

1. The target article makes a restrictive interpretation of the *latent variable models*. Along the article's lines, latent variable models are represented as *unidirectional* trees, the "latent variable" (the common cause) being the root. In this representation, the authors assume that all links have the same importance. Yet, by definition, a latent variable is only non-observable, and is not necessarily causally central. Cramer et al. are probably right in criticizing the assumption (implicit in psychiatry) that all symptoms should be related to a *central* latent variable, but they mistakenly underestimate the potential role of *accessory* latent variables. Getting rid of all latent variables would be tantamount to assuming that everything is known about the observed phenomenon. Moreover, there is no reason why the flexibility they claim for their network approach (multi-directionality, different link strength) should not be allowed within the context of a latent variable model.

2. Besides, a heuristically good reason to suppose the existence of a latent variable is mainly therapeutic rather than methodological. This kind of hidden variable is often seen as a therapeutic target rather than an etiological node; that is, not something to find that would explain everything, but something to act upon that would dissolve everything. If a match is considered *the* cause of a fire in a building, rather than oxygen in the air, which is no less required to start a fire, it is because the match seems the most appropriate factor to act upon. Mackie (1974), Hesslow (1984), Gannett (1999), and Magnus (1992), among others, have shown the importance of pragmatic concerns in the search for a single target which might be called *the* cause of a disease (it is called the problem of *causal selection*). This kind of pragmatic interpretation of a latent variable as "what we have to act upon" may justify the otherwise objectionable assumption that there is actually a latent variable which explains and causes everything. There is, however, a question as to how the network approach is to be translated into the definition of therapeutic targets. For instance, while such a definition is obviously easy on the basis of the target article's Figure 1, one might ask what could be proposed on the basis of Figure 4.

3. It would also be interesting to discuss this model, as well as the latent variable model, with regard to the biological markers of these diseases. Indeed, particular markers of the disorder could be related to specific biological alterations. For example, anhedonia could be related to a deficit in nucleus accumbens processing, or a defect in stress reactivity to a dysregulated neuroendocrine axis.

4. Beyond that, in the case of two comorbid disorders, do the authors propose that each symptomatic node be related to a specific biological dysfunction that would be common to the two comorbid pathologies? In this case, a given biological marker defect underlying pathology A would also be altered in the comorbid pathology B. If there is no latent variable underlying the different symptomatic features, what is the explanation as to why these symptoms often co-occur? Moreover, if two comorbid disorders have a common epiphenomenal symptom, should this be regarded as a *bridge symptom*? For example, if decreased eating occurs in an anxiety disorder as well as in depression, but does not induce (or is unrelated to) any of the other symptoms of depression or anxiety, might it not be considered a bridge symptom underlying comorbidity? How can symptoms be distinguished from "non-symptom causal processes" (sect. 2, para. 9) or from the "external effects" (sect. 5, para. 6) if the boundaries of the disorders are "fuzzy" (sect. 6, para. 6)?

5. It would be interesting to compare the network model described by Cramer et al. with the psychopathological endophenotype approach that has been developed to dissect major depression into different independent entities (see, e.g., Hasler et al. 2004), or with other constructs used in the field of psychiatry, such as connectionist-inspired ones (e.g., Tanti & Belzung 2010).

The rocky road from Axis I to Axis II: Extending the network model of diagnostic comorbidity to personality pathology

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Abstract: Although the network model represents a promising new approach to conceptualizing comorbidity in psychiatric diagnosis, the model applies most directly to Axis I symptom disorders; the degree to which the model generalizes to Axis II disorders remains open to question. This commentary addresses that issue, discussing opportunities and challenges in applying the network model to *DSM*-diagnosed personality pathology.

Cramer et al.'s network model represents a promising new approach for conceptualizing and quantifying comorbidity in psychiatric diagnosis, helping avoid the thorny challenge of operationalizing latent constructs, and shifting the focus of comorbidity research from syndrome to symptom. Scrutiny of Cramer et al.'s analysis reveals that the theoretical underpinnings and empirical evidence bearing on this model apply most directly to Axis I symptom disorders (e.g., major depression, generalized anxiety). Because Axis II personality disorders differ in myriad ways from Axis I symptom disorders, the degree to which the network comorbidity model generalizes to Axis II disorders remains open to question. This commentary addresses that issue, discussing issues that arise in applying the network model to *DSM*-diagnosed personality pathology (i.e., the personality disorder [PD] diagnoses offered in the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* or *DSM-IV*; American Psychiatric Association 1994).

As Cramer et al. have noted, diagnostic comorbidity evidence involving *DSM-IV* Axis I disorders can yield ambiguous, confusing patterns. Diagnostic comorbidity evidence bearing on *DSM-IV* Axis II is far worse. Consider: The number of differential diagnoses per *DSM-IV* PD ranges from 3 (dependent, obsessive-compulsive) to 7 (paranoid), with the mean number of differential diagnoses per PD being 4.5. Thus, on average each *DSM-IV* PD shows substantial overlap with 50% of the remaining PDs. When Ekselius et al. (1994) calculated correlations among interview-derived scores for PDs in a heterogeneous sample of psychiatric patients and nonclinical participants, they obtained a mean interscale correlation (r) of .41, and statistically significant interscale correlations in 41 of 45 comparisons (91%). Subsequent comorbidity studies have confirmed these results (Bornstein 1998; 2005).

Given these patterns, extending the network comorbidity model to Axis II presents some unique challenges, but it also involves some unique opportunities to gain new perspective on

the model, its advantages, and its limitations. Two issues are germane in this context.

1. PD symptoms differ fundamentally from Axis I symptoms. Axis I disorders are sometimes called "symptom disorders" because they are characterized by prominent, psychologically painful symptoms (e.g., depressed mood, difficulty sleeping, binge eating). Whether or not patients choose to acknowledge them when asked, they are typically aware of experiencing these symptoms (even if not fully aware of the symptoms' negative impact). The situation is very different for Axis II PDs, which have traditionally been conceptualized as being "ego syntonic" (i.e., consistent with the patient's experience of self). As a result, personality-disordered patients typically have far less insight into their symptoms than do patients with Axis I disorders, which complicates diagnosis, decreases motivation for treatment, and reduces therapeutic efficacy (Peters 1990; Shedler & Westen 1999).

In the context of the network model, these Axis I–Axis II differences have two noteworthy implications. First, although self-report assessment tools (e.g., questionnaires, diagnostic interviews) are the measures of choice for rendering Axis I diagnoses, such measures are of limited value in rendering Axis II diagnoses (see, e.g., Widiger & Samuel 2005). Indirect measures (e.g., free-response tests) and reports from knowledgeable informants must be used in conjunction with self-report instruments to assess PDs reliably (Bornstein 2007).

Second, these Axis I–Axis II differences in insight and self-awareness suggest that the definition of *latent variable* as conceptualized in the network model must be expanded when applied to Axis II. Here it is not only necessary to distinguish observable symptoms from unobservable latent constructs, as the network model suggests, but also to distinguish symptoms that are *phenomenologically latent* (i.e., ego syntonic) from those that are experienced as problematic by the patient (i.e., ego dystonic).

2. Unlike Axis I criteria, Axis II criteria are revised to minimize comorbidity. In many clinical settings the most common Axis II diagnosis is "mixed PD," and epidemiological data indicate that a sizeable proportion of PD-diagnosed patients – more than 50% in some samples – receive two or more PD diagnoses (Bornstein 2003; Widiger & Clark 2000). As a result, symptom revision across successive editions of the *DSM* entails somewhat different goals on Axis I and Axis II. On Axis I symptoms are revised to increase diagnostic accuracy, but on Axis II symptoms are revised to maximize accuracy while simultaneously reducing comorbidity.

As I have noted elsewhere (Bornstein 2003), when Axis II symptoms are reworded or removed merely to limit escalating comorbidity rates, clinicians are choosing to alter reality (i.e., a high level of PD comorbidity) to fit some idealized conceptualization of PDs as distinct and separate syndromes. For example, "frantic efforts to avoid real or imagined abandonment" (see *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised* [*DSM-III-R*]; American Psychiatric Association 1987, p. 347) was removed from the dependent PD criteria in *DSM-IV* because patients with borderline PD also show this symptom, but every extant model of dependent PD would argue for inclusion of this symptom (Bornstein 2005). Removing certain PD symptoms merely to minimize PD overlap is akin to arguing that labored breathing should no longer be considered a symptom of pneumonia because patients with emphysema also show this symptom. Clearly, the contrasting strategies used to revise symptoms on Axis I and Axis II present a challenge when the network comorbidity model is extended from symptom disorders to personality pathology.

Without question, Cramer et al.'s network model represents a promising new approach to conceptualizing and quantifying comorbidity in psychiatric diagnosis. This perspective not only captures dynamic features of psychopathology that traditional latent variable models cannot capture, but has the additional advantages of shifting the focus from surface behavior to underlying process, and the level of analysis from syndrome to symptom. Extending the network model to Axis II will be challenging, but likely to benefit the model over the long term by compelling researchers to confront conceptual and empirical challenges that do not arise when the model is applied to Axis I. Questions regarding the generalizability of symptom clusters, nodes, and bridge symptoms across culture, age, and gender are almost certain to emerge, and as research on the network model advances, it will not only be useful to extend this model from Axis I to Axis II, but to begin to address aspects of cross-axis comorbidity as well.

Aligning psychological assessment with psychological science

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Abstract: Network analysis is a promising step forward in efforts to align psychological assessment with explanatory theory in psychological science. The implications of Cramer et al.'s analysis are quite general. Networks analysis may illuminate functional relations not only among observable behaviors that comprise psychological disorders, but among cognitive and affective processes that causally contribute to everyday experience and action.

One of contemporary psychology's more curious features, long noted (Cervone 1991; Mischel 1973), is that the strategies through which investigators pursue two of the fields' primary goals are discordant. One goal is to understand the workings of the mind. Although there may be disagreement on the details – the precise nature of mental mechanisms and abilities, and the degree to which they are innately specified or developed through interaction with the physical and social world – there is consensus at a broad strategic level. The mind is a complex system of distinct yet functionally related parts (e.g., Barsalou 1999; McClelland & Rogers 2003). Multiple interacting subsystems, both cognitive and affective, contribute to experience and action (Cervone 2004; Mischel & Shoda 1995; Sander et al. 2005). "Observable behavior is an interaction effect par excellence" (Fodor 1983, p. 1).

The other goal is to assess qualities of the individual. Assessment efforts commonly describe people with respect to constructs identified in latent variable analyses. In clinical diagnosis, the constructs are diagnostic categories. In personality trait psychology, they are dimensions (Costa & McCrae 1992). In either case, as Cramer et al. highlight, the *common cause* hypothesis of latent variable modeling dictates that the observable behaviors indicative of a given category or dimension are not functionally related to one another. Local independence among the indicators is assumed.

At the level of substantive theory, few psychologists are likely to embrace the common cause hypothesis and its consequences. Clinicians commonly reject essentialist views in which a diagnostic category corresponds to a singular cause (Ahn et al. 2006). Investigators who employ latent variable modeling in their research may, when pressed, abandon its common cause assumptions on theoretical grounds (see Cervone et al. 2006). "Problem and method," then, "pass one another by" (Wittgenstein 1953/2001, p. 197). Even investigators who recognize that actions, affects, and cognitions interact adopt latent variable methods that obscure these interactions from view.

The resulting conceptual contrast is just as sharp as Cramer et al. suggest. Consider a standard psychological science

account of a person's tendencies to experience emotions such as anxiety and fear ("symptoms," in the case of disorders). The affective scientist might explain them by reference to interactions among physiology, cognitive appraisals processes, and enduring beliefs (e.g., Sander et al. 2005). A developmentalist would add that temperament, which itself develops partly through environmental interaction, contributes to this interacting system of cognitive and affective elements (Schmidt & Fox 2002). Importantly, in any such account, emotional tendencies such as anxiety and fear are the *explananda*, the phenomena to be explained. The interacting mental systems are the *explanans*.

The latent variable approach turns this world upside down (Cervone 1999). In comorbidity analyses, the high-level psychological tendency "internalizing" (Krueger 1999) does explanatory work: It explains correlations among lower-level locally independent tendencies such as anxiety and fear. The tendencies to experience anxiety and fear, in turn, do more explanatory work: They explain correlations among yet lower-level locally independent tendencies such as the experience of panic and social anxiety. And so it goes; it is locally independent tendencies all the way down. Not only are there no interactions among indicators of a given construct; there also is no explanation of experience and action by reference to well-defined systems of mind or brain.

This might be palatable if investigators were careful to describe latent variables merely as clusters of interrelated behaviors. But, instead, they commonly discuss them in terms normally reserved for structural entities with causal power (Cervone 2005). For example, *internalizing*, a construct that summarizes between-person correlations among indices of psychological distress, is said to be a "substrate" (Krueger 1999, p. 926) of mental disorders. This is not unlike a geologist positing a substratum of "destructiveness forcefulness" to explain a region's tendency to experience both volcanoes and earthquakes.

Explanations that reference abstract tendencies of the sort identified in latent variable analyses are seductive (Kagan 1998) – so much so that, once, even Cramer et al. are enticed. Did they really mean to say that "neuroticism" – a latent variable that reflects intercorrelations among dispositional tendencies to experience anxiety, hostility, self-consciousness, impulsiveness, vulnerability, and depression (Costa & McCrae 1992) – "can *trigger* the onset of depression" (sect. 4, para. 5, emphasis added)? Neuroticism is ripe for network analysis. One would not claim that it "triggers" depression, since depression is part of neuroticism, and neuroticism is conceptualized as a constant (see Borsboom et al. 2003).

The great virtue of Cramer et al.'s article is that they not only articulate a problem, but provide a solution: network analysis. Future work might expand their current scope. In principle, networks could include functional relations not only among observable behaviors, but among cognitive and affective components as well; empirical evidence documents numerous functional relations, such as the influence of self-consciousness on emotion (Mor & Winquist 2002), self-efficacy perceptions on motivation (Bandura 1997), knowledge structures on self-appraisals (Cervone et al. 2008), and mood on self-evaluations (Cervone et al. 1994). One might account for personality traits in the manner Cramer et al. account for diagnostic categories and comorbidities. Functional relations among perceived self-efficacy, personal goal-setting, and disciplined, persistent behavior (e.g., Bandura & Cervone 1986), for example, might enable one to view conscientiousness (whose components include competence, achievement striving, self-discipline, and dutifulness; Costa & McCrae 1992) as a cluster of functionally interrelated cognitive–affect elements and their behavioral effects.

Such an effort requires an assessment method that taps these cognitive and affective elements. A social-cognitive approach to assessment (Cervone et al. 2001) is apt in that it addresses "functional relations among affect and physiological arousal, cognition, and action" (Cervone et al. 2001, p. 41) rather than latent variables measured by independent indicators. Social-cognitive methods, and recent clinical assessment efforts (Haynes et al. 2009), are sensitive to individual idiosyncrasy, thus addressing Cramer et al.'s recognition of possible individual-level variability in network structure.

For more than four decades, psychologists have called for assessment and measurement strategies that align with the body of knowledge available in psychological science (Mischel 1968). Cramer et al.'s contribution is a most valuable step in this direction.

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Comorbid science?[1]

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Abstract: We agree with Cramer et al.'s goal of the discovery of causal relationships, but we argue that the authors' characterization of latent variable models (as deployed for such purposes) overlooks a wealth of extant possibilities. We provide a preliminary analysis of their data, using existing algorithms for causal inference and for the specification of latent variable models.

We agree with the view that Cramer et al. develop in the target article: that naïve latent variable models often fall woefully short of ideal. Unfortunately, their proposed solution and accompanying test case suffer from a number of flaws.

Cramer et al. begin with a straw man: They assume that, in a latent variable model, symptoms cannot also influence one another. Unless we define "latent variable model" to exclude such effects, there is no reason to impose such a constraint on our models. Mathematically, it is straightforward for latent variable models to have both latent common causes of measured variables and direct influences of measured variables on other measured variables. This is often the case for actual causal structures; for example, when there is confounding in observational or quasi-experimental studies.

Cramer et al. further claim that a "latent variable model renders all symptoms equally central and thus exchangeable" (sect. 5, para. 3). This claim is difficult to understand. "Central" is neither a causal nor a statistical notion; "exchangeable" is a statistical notion that, if meant, would be quite inappropriate in this usage. Cramer et al. might mean that in latent variable models all symptoms have the same variance, or the same dependence on any latent variables, or in their probability distributions conditional on values of latent variables, or in their probabilities conditional on one another. Each of these claims is violated in many latent variable models in the social sciences and elsewhere, and all of these claims are false unless "latent variable model" is arbitrarily defined so as to satisfy them. But that would be to focus on

a model class that no one ought to accept a priori in the first place.

Cramer et al. focus on a stiff but appropriate standard for (their version of) latent variable models: The models should get the causal relations right. Unfortunately, they do not apply that same standard to their favored alternative. Instead, they resort to representing simple associations, with occasional suggestions that the relationships they so specify could be causal (e.g., sleep deprivation causes tiredness). Simple associations cannot, in general, be used reliably to estimate causal relations: they ignore possible screening off (conditional independence) relations, measurement errors, and latent confounding, and they give no direction to causal relations when they exist. Cramer et al. focus on two extreme model classes and ignore the enormous space of (learnable and estimable) models that lie between these poles; those models can include all of latent variables, direct causal connections, and feedback cycles (of varying speeds).

Consider instead searching for graphical causal models from their data. Absent latent variables, graphical causal models – both cyclic and acyclic – specify conditional independence relations. These relations can be used to search for cyclic and acyclic causal models. The theory of cyclic graphical models is difficult and underdeveloped, and for binary variables no adequate search procedure is available, but the target article does not engage what *is* known (e.g., Lacerda et al. 2008; Pearl & Dechter 1996; Richardson 1996). For acyclic graphs, there are many correct search algorithms (e.g., PC, Spirtes & Glymour 1991; FCI, Spirtes et al. 1993; Conservative PC or CPC, Ramsey et al. 2006; Greedy Equivalence Search [GES], Meek 1997). The PC algorithm, for example, is an asymptotically pointwise consistent search procedure under independent and identically distributed (i.i.d.) sampling when there are no latent variables and the structure is acyclic. The PC algorithm will sometimes return double-headed arrows; asymptotically, the appearance of such structures in the PC output indicates latent common causes of the connected variables. We can at least begin to explore the possibilities with PC.

The data that Cramer et al. use to illustrate their approach are missing more than 70% of the possible values, and there is no explanation in their article of how those missing values are treated. There are several possibilities: A search can be conducted using only cases with no missing values, but that would include only about 10% of the cases; missing values can be replaced at random according to some prior distribution; missing values for a variable can be replaced using a probability distribution equal to the frequency distribution of that variable in the available data; or, as in the PC algorithm, relevant statistics can be computed using available data and ignoring missing values. For the data Cramer et al. provide, and a .05 alpha value for conditional independence decisions, the PC algorithm yields the graph in Figure 1:

The variables form three distinct clusters: The larger two correspond to the two focal diagnostic categories, connected only by the two measures of sleep. The MDD (major depressive disorders network) measures form two disconnected components. Four variables (gSleep, gConc, gFatig, gIrri) form a chain of double-headed arrows, suggesting that there may be an unobserved common cause. The BPC (Build Pure Clusters) search algorithm (Silva et al. 2006) estimates whether a set of variables shares a latent common cause; BPC is asymptotically correct for binary variables whose values are two-valued projections of a Gaussian distribution. BPC finds that gSleep, gConc, gFatig, and gIrri do have a latent common cause, as do a separate cluster of MDD measures (mRep, mRest, mSuic). Similar results are found if missing values are replaced using the base frequency of each variable value.

This analysis is scarcely complete. For example, were the data good enough to warrant it, one could apply the FCI (Fast Causal Inference) algorithm (Spirtes et al. 1993), which is correct when there are both latent common causes and direct influences of measured variables on one another.

In our view, Cramer et al. unnecessarily restrict the modeling options, do not offer a plausible, reliable method for causal inference, and fail to explore what the data from their own example might reveal.

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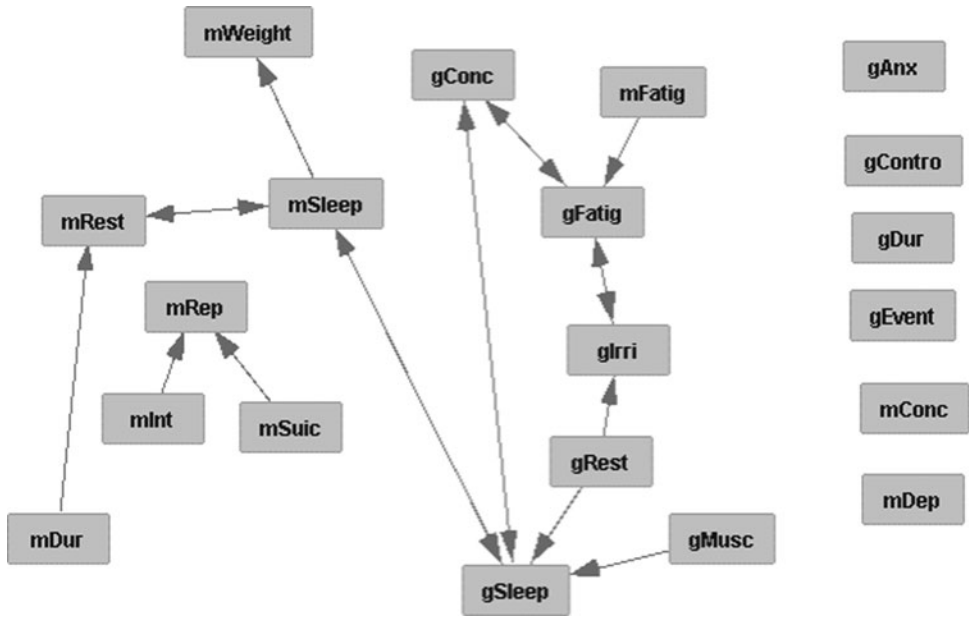

Figure 1 (Danks et al.). PC output for Cramer et al.'s data

NOTE

1. Authors are listed in alphabetical order; all contributed equally to this commentary.

Visualizing genetic similarity at the symptom level: The example of learning disabilities

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Abstract: Psychological traits and disorders are often interrelated through shared genetic influences. A combination of maximum-likelihood structural equation modelling and multidimensional scaling enables us to open a window onto the genetic architecture at the symptom level, rather than at the level of latent genetic factors. We illustrate this approach using a study of cognitive abilities involving over 5,000 pairs of twins.

A surprising finding emerging from genetic studies across diverse learning disabilities is that most genetic influences are shared: They are "generalist" rather than "specialist" (Plomin & Kovas 2005). We know this because multivariate genetic analysis of twins yields genetic and environmental correlations among traits; high genetic correlations point to a shared genetic etiology and frame a "generalist genes" hypothesis. Although recent advances in molecular genetics, such as genome-wide association, are revealing the genetic variants that are responsible for these common influences (Wellcome Trust Case Control Consortium 2007), we are beginning to realize that the genetic and environmental architecture of psychological traits is far more complex than previously imagined. Just as Cramer et al. highlight the difficulties of psychiatric diagnosis at a phenotypic level, we have argued that, at an etiological level, such common disorders are quantitative traits reflecting multiple underlying dimensions of genetic (and environmental) risk (Plomin et al. 2009). To maximize our chances of identifying particular genetic variants, it is essential that we understand the genetic relationships among these traits by estimating and comparing the genetic correlations derived from genetically sensitive study designs (Plomin et al. 2008). In common with Cramer et al., we have found that one of the most effective ways to present and reason about such high-dimensional information is through graphical representation (Tufte 2001).

Accurate estimation of multivariate statistics such as genetic and environmental correlations requires large samples. We recently exploited widespread access to inexpensive and fast Internet connections in the United Kingdom to assess over 5,000 pairs of 12-year-old twins from the Twins Early Development Study

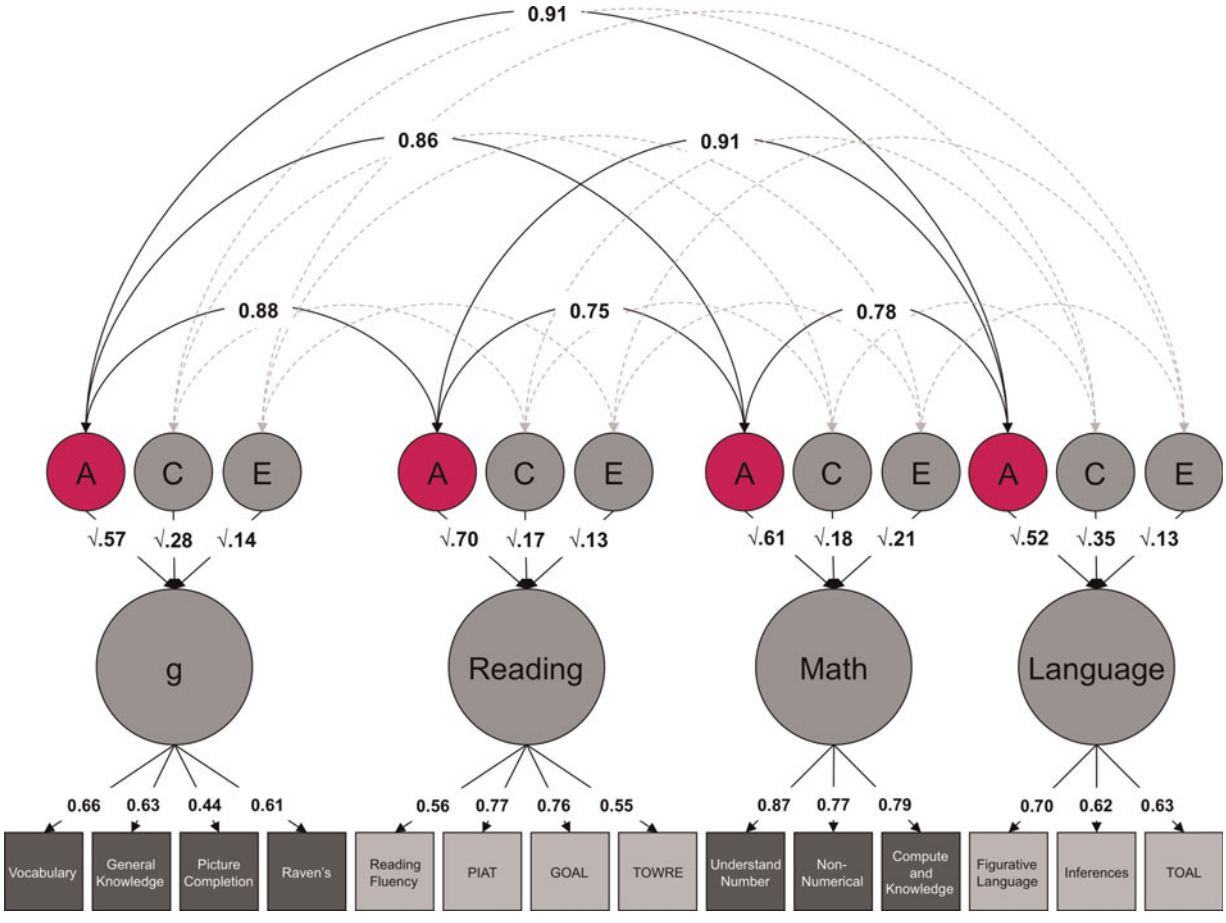

Figure 1 (Davis and Plomin). Latent factor twin model with genetic correlations highlighted: A, additive genetic effects; C, shared (common) environmental effects; and E, nonshared environmental effects. Squares represent measured traits, and circles represent latent factors. The lower tier of arrows represents factor loadings, and the second tier represents genetic and environmental path coefficients. The curved arrows at the top represent correlations between genetic (solid lines) and environmental (dotted lines) latent factors. Adapted from Davis et al. (2009).

(TEDS; Oliver & Plomin 2007) on four batteries: reading, mathematics, general cognitive ability (*g*), and, for the first time, language (Haworth et al. 2007). A multivariate structural equation model using latent factors showed that, as expected, genetic correlations among reading, mathematics, and *g* are high in late childhood and early adolescence (0.75–0.91), with language as highly correlated genetically with *g* as reading and mathematics (see our Fig. 1 here) (Davis et al. 2009).

However, as Cramer et al. demonstrate, there is another level of detail that cannot be investigated through analysis of latent factors. The batteries that index the latent constructs of reading, mathematics, *g*, and language can be broken down into their constituent tests, our "symptoms," to better understand the complex relationships among cognitive components that result in high correlations at the level of latent factors. Our own approach to exploring these relationships used multidimensional scaling of genetic correlation matrices to produce interactive graphical representations of the underlying genetic architecture.

As shown in Figure 1, each latent construct was characterised by three or four subscales that assessed different aspects of the trait: 14 tests in total. These measures are described in detail in Davis et al. (2009). Multidimensional scaling can be used to reduce the high-dimensional relationships among the tests to two or three spatial dimensions.

Classical (metric) multidimensional scaling (Gower 1966; Young & Householder 1938) requires a matrix representing the pair-wise "distance" between every pair of traits. With a high-performance computing cluster we calculated the pair-wise genetic correlations among all the tests in the battery using maximum-likelihood structural equation model-fitting in *Mx* (Neale et al. 2006) to make a genetic correlation matrix. The genetic correlation matrix represents the genetic similarity among the tests. To represent the genetic *dissimilarity*, or distance, we subtracted the correlations in the matrix from 1. We performed multidimensional scaling on the resulting matrix using the *R* function *cmdscale* (*R* version 2.10.1; *R* Development Core Team, 2009) and checked whether three dimensions allowed an adequate representation of the true distance matrix using the criterion suggested by Mardia et al. (1979) and inspection of a Shepard diagram, which plots the distances obtained from multidimensional scaling against the values in the original distance matrix.

Figure 2 represents the well-fitting three-dimensional solution using the graphics library OpenGL, available in *R* through the *rgl* package. The screenshot shows genetically similar traits clustering together and genetically dissimilar traits more distant from one another in space. For a sense of scale, the closest relationship is between two measures of reading comprehension, GOAL and PIAT in the centre of the figure, with a genetic correlation of almost 1; the most distant relationship (a genetic correlation of 0.12) is between TOWRE on the far left, a measure of reading fluency, and Picture Completion on the far right, a measure of nonverbal ability. The image highlights subtle patterns of gene-sharing among the tests. For example, the mathematics tests cluster close together, while the comprehension and fluency components of reading ability are relatively separate in the centre and far left. Likewise, the *g* battery falls naturally into verbal (near the top) and nonverbal (far right) components. Meanwhile, reading comprehension, the verbal components of *g*, and language cluster at the top of the figure. Although most correlations are strong, the heterogeneity tells a more nuanced version of the *generalist genes* story than we saw at the level of latent factors.

This approach to visualizing the genetic relationship among traits at the symptom level complements Cramer et al.'s network approach to phenotypic comorbidity. When they call for scholars from a wide variety of disciplines to join together to fashion a new approach to psychometrics, they may certainly count geneticists among their allies.

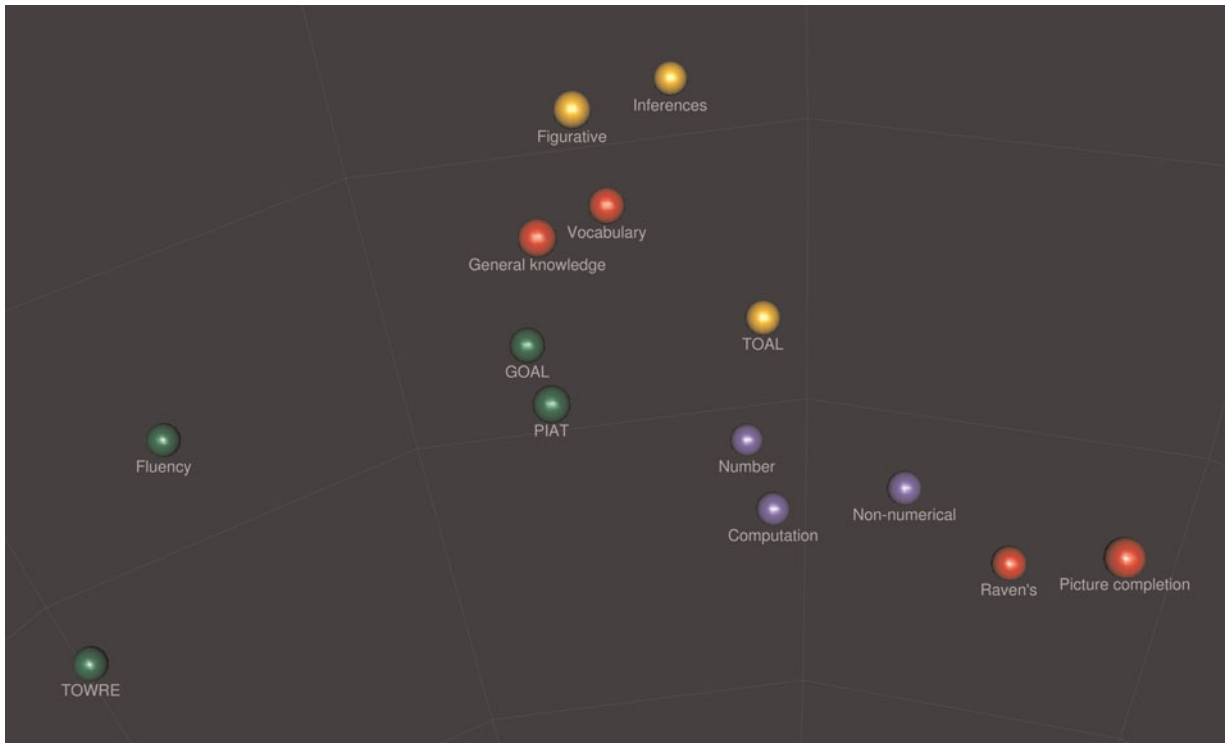

Figure 2 (Davis and Plomin). Screenshot of a three-dimensional representation of genetic similarities among the tests that form the latent factors in Figure 1. Each sphere represents a test, and tests are colored by corresponding latent factor from Figure 1: green for reading, blue for mathematics, red for *g*, and yellow for language. Tests with similar genetic influences are closer together in space.

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An agenda for symptom-based research

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Abstract: The network approach proposed by Cramer et al. suggests fascinating new directions of research on mental disorders. Research is needed to find evidence for the causal power of symptoms, to examine symptoms thoroughly, to investigate individual differences in edge strength, to discover etiological processes for each symptom, and to determine whether and why symptoms cohere into distinct mental disorders.

The network approach proposed by Cramer et al. suggests fascinating new directions of research on mental disorders. This commentary highlights the advantages of the target article's approach and proposes directions for research supporting it. In particular, the proposition that symptoms causally affect one another, rather than being mere signs or outcomes of an underlying latent disorder, is exciting. Although symptoms would be powerful even as mere outcomes (e.g., by being intensely aversive for self or others), ascribing causal power to symptoms raises them to an even greater level of importance as the very heart of psychological disorders.

1. Find evidence for the causal power of symptoms. An urgent line of research is to test the proposal that symptoms have causal power for other symptoms. Although the network approach presented by the target article is plausible, we believe that this proposal has yet to be supported by sufficient empirical evidence. The most directly relevant evidence would be a demonstration of the causal power of symptoms. Evidence for the causal power of symptoms could be obtained from cross-lagged effects, either long-term effects from longitudinal designs or short-term effects from experience-sampling studies (Conner et al. 2009). Evidence for causality might even be obtained from experimental manipulation of symptoms (if ethical and minimally distressing).

Recent research on "normal" personality has taken a similar line. For example, extraversion and positive affect are robustly correlated (Lucas et al. 2000), which is often interpreted as resulting from a latent extraversion trait factor causing a latent positive affect trait factor. One of us has conducted experiments showing instead that state manifestations of extraversion (becoming extraverted for a moment, analogous to a disorder's symptom) cause the state of positive affect (McNiel & Fleeson 2006). That is, the states of normal traits have causal power, suggesting that the symptoms of mental disorders may also have causal power, and that manipulating them in experiments or tracking their lagged effects in experience-sampling studies may be fruitful.

2. Examine symptoms thoroughly. The network approach suggests a more thorough assessment of symptoms. If symptoms are more than indicators, then their patterns and frequencies of occurrence should be assessed. For example, experience-sampling studies, in which participants report symptoms every few hours for a few weeks, would provide rich information about the frequencies, patterns, and co-occurrences of symptoms (i.e., evidence of symptom co-occurrences for a given person across time or situations). This information is key for determining node strength and edge strength in the network. For example, the frequencies and co-occurrences of emotional volatility (Trull et al. 2008), idealization, suicidal ideation, and emptiness on a daily basis could help determine the node strengths and edge strengths in Borderline Personality Disorder (BPD)

3. Investigate individual differences in edge strength. The incorporation of edges or connections between symptoms opens up new possibilities for the conceptual definitions of disorders and of diagnosis. Rather than individual differences in the levels of the symptoms being the primary component of a disorder, individual differences in the interconnections among symptoms may become an additional or central component to the disorder. If symptoms affect one another, then different people might have different strengths of causation linking symptoms. For example, some people might have a strong connection between perceived feelings of abandonment and self-injury, such that abandonment is usually followed quickly by self-injury, whereas others may have a weak connection between these symptoms. Such individual differences in strengths of connections between symptoms might determine whether a given individual experiences only one symptom or descends into a cascade of mutually activated symptoms; since the difference between these two outcomes comes from the strength of the connections, it might mean that having the disorder or not is a matter of having or not having strong connections. That is, everyone might be vulnerable to occasional symptoms (e.g., anger, perceptions of rejection), but only some may show an entire collection of symptoms.

Carried still further, it is possible that different individuals, all with relatively strong edges among some symptoms of a disorder, nonetheless differ in which edges are strongest. Thus, they all suffer a cascade of symptoms when any one symptom is activated, but they suffer different cascades from each other. This kind of heterogeneity in symptoms would be identified by within-person analyses of experience-sampling data, which would reveal individual differences in co-occurrences of symptoms, and aid in risk assessment.

4. Discover etiological processes for each symptom. If there were only one causal factor for a mental disorder, then it would be more plausible that there is only one etiological process for that mental disorder; namely, the one that produces the latent factor within the individual. However, if each symptom has causal power to set up a chain of consequences, then each symptom likely has its own etiological history. Research that identifies the triggers and processes resulting in each symptom would be useful. Again, experience-sampling data would reveal co-occurrences between triggers and symptoms.

5. Determine whether and why symptoms cohere into distinct mental disorders. A concern about the network approach is that, without single latent causes, disorders may lose coherence and become replaced by countless individual symptoms, creating a situation too chaotic for research or for treatment. Cramer et al. have proposed some plausible technical rules for identifying coherent disorders, but they have not provided evidence that such rules produced distinct clusters or disorders. Thus, it is necessary to determine whether those rules produce coherence, whether other rules are needed, or whether distinct disorders are hard to identify. Distinct disorders may also arise from multiple, small latent causes, which affect each other causally.

We are embarking on a 5-year project on the symptoms of BPD that undertakes some of these lines of research. The evidence for or against the network approach is still to be produced, but we are convinced that the approach supports lines of research that are likely to produce new important insights into disorders. In turn, this should lead to new treatments focused on the causal power of symptoms.

Extending the network perspective on comorbidity

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Abstract: Cramer et al. make a good case for reconceptualizing comorbid psychopathologies in terms of complex network theory. We suggest the need for an extension of their network model to include reference to latent causes. We also draw attention to a neglected approach to theory appraisal that might usefully be incorporated into the methodology of network theory.

Despite its prominence in clinical research, the concept of comorbidity is heavily contested (e.g., Lilienfeld et al. 1994). In the target article, Cramer et al. contend that the major problem with comorbidity research stems from its widespread adoption of standard latent variable theory, which holds that latent variables are common causes that explain the correlations between the manifest variables to which they give rise. On this view, comorbidity is a bidirectional relation between latent variables that causally produce correlated indicator variables or symptoms. The problem arises from the model's acceptance of the statistical assumption of local independence, which says that the manifest indicators are solely due to the influences of the common causes; they cannot relate to one another causally. We are unsure how widespread in comorbidity research this latent variable theory actually is, but we agree with Cramer et al. that its inability to allow manifest variables or symptoms to be causally related is a major limitation of its conceptualization of comorbidity.

Cramer et al.'s alternative conceptualization of comorbidity as complex networks of causally related symptoms holds considerable promise for resolving some troubling issues in the field, and the authors point to several advantages that this perspective holds. A major achievement of the target article is its demonstration that network theory has the resources to help resolve several syndromal questions about comorbidity (see also Meehl 2001).

Cramer et al.'s network depiction of comorbidity has no place for latent variables as common causes. In fact, as it is currently formulated, their model has no place for latent variables at all. The result is a "flat" model of comorbidity that embraces only manifest symptoms in causal relation to one another. However, this particular feature of the model should be seen as a contingent feature of its initial formulation, not as an expression of an unyielding empiricist commitment to focus on the phenomenology of psychopathology only. The authors make clear that their network characterization of comorbidity is necessarily incomplete. They explicitly acknowledge that relations between symptoms are likely to be mediated by other unobservable (i.e., latent) factors in causal chains. Of course, to embrace latent factors in an extended network model would not be to admit common cause latent variable theory back into the fold. But it is perhaps worth noting here that there are alternative nonstandard models within latent variable theory that permit the specification of different relations between latent and/or manifest variables. For example, Keith Markus has suggested to us in personal communication that there are no good theoretical and statistical reasons why one could not insert direct causal paths between indicator variables in a structural equation model.

We think that further research on network formulations of psychopathologies is justified on strategic methodological grounds, and should now be extended to explicitly incorporate reference to etiological factors at whatever level of specificity can be achieved. Despite the use of latent variable models in research on psychopathology, there is a general distrust of theorizing about latent causes by researchers in the field. The largely atheoretical nature of the *DSM*s III and IV (*Diagnostic and Statistical Manual of Mental Disorders*, 3rd and 4th editions; American Psychiatric Association 1987; 1994), for example, came about because their task forces believed that good causal theories of psychopathology were seldom to be had. We think the construction of explanatory theories of comorbid conditions should be pursued with vigour. Good theories are to be valued because they are our primary vehicles for understanding the relevant syndromal facts. However, this will require the implementations of sound theory construction strategies. Psychology, with its penchant for the weak testing of austere theories via tests of statistical significance, and an overreliance on goodness-of-fit measures of empirical adequacy, has been somewhat remiss in this regard. Relatedly, there has been a general failure to acknowledge that good theories in science are often generated by abductive or explanatory means in order to explain established phenomena, developed through a strategy of analogical modeling, and evaluated on multiple criteria, some of which have to do with the explanatory worth of theories (Haig 2005; for an application of abductive theory construction methods to clinical reasoning and case formulation, see Vertue & Haig 2008).

In a preliminary test of their hypothesis about the importance of bridge principles in explaining comorbidity, Cramer et al. use the Akaike information criterion to judge the fit of competing models. This can be seen as one approach to the widespread practice in science of testing hypotheses about models for their predictive accuracy. However, the inclusion of latent factors in a network model of comorbidity raises the question of how one should evaluate those models when they contain explanatory hypotheses. Cramer et al. rightly point out that common cause latent variable theories have modest explanatory power. However, network theories that appeal to latent causes more generally have the potential to offer more powerful explanations. Their evaluation will have to combine information about postulated causes (preferably in the form of causal mechanisms), correlations, and competing causal accounts. An approach to theory evaluation that can do this is known as *inference to the best explanation* (see Haig 2009). With inference to the best explanation, the ideas of explanation and evidence come together, and explanatory reasoning becomes the basis for evaluating theories: The explanatory goodness of theories counts in their favour. Conversely, the explanatory failings of theories detract from their credibility. According to Thagard (1992), inference to the best explanation is essentially a matter of establishing relations of explanatory coherence between propositions within a theory. To infer that a theory is the best explanation is to judge it as more explanatorily coherent than its rivals. Theories depicted as networks of propositions, including network models of comorbidity, lend themselves naturally to evaluation in terms of considerations of explanatory coherence.

In conclusion, we think the long-term prospects of network theory in psychopathological research are good precisely because it can exploit the considerable conceptual and investigative resources of dynamical systems theory. Cramer et al.'s dynamical systems conceptualization of comorbidity can study change in individuals over time. It therefore promises to feature in a future clinical psychology that has moved beyond the strictures of the present *DSM* model to embrace, among other things, an idiographic, process-oriented approach to scientific research on comorbidity and other psychopathologies.

Symptom networks and psychiatric categories

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Abstract: The network approach to psychiatric phenomena has the potential to clarify and enhance psychiatric diagnosis and classification. However, its generally well-justified anti-essentialism views psychiatric disorders as invariably fuzzy and arbitrary, and overlooks the likelihood that the domain includes some latent categories. Network models misrepresent these categories, and fail to recognize that some comorbidity may represent valid co-occurrence of discrete conditions.

Cramer et al.'s network perspective is a welcome innovation in a field whose problems and practices are equally stubborn. As a methodological tool, network analysis could enhance psychiatric diagnosis by clarifying symptom centrality and improve classification by mapping the "symptom space" in ways that may reduce comorbidity. The network perspective also provides an appealing rationale for paying attention to symptoms as phenomena that matter in themselves rather than merely being superficial and causally impotent markers of reified "disease entities" (Hyman 2010). This ontological upgrading of symptoms would be popular with behavioral clinicians (Persons 1986), whose treatments directly target symptoms and who tend to find talk of "latent variables" a little beside the point. Indeed, I suspect that many clinicians would agree with the authors in comprehending mental disorders as constituted by their symptoms rather than revealed in them. Diagnostic labels are often treated as useful shorthands, rather than as natural kind terms.

Although focusing attention on symptoms and their interrelations has scientific and clinical advantages, it is questionable to go further and rule out in principle the existence of latent psychopathologies. Cramer et al.'s elimination of latent variables goes too far, and as a result the authors' account overreaches. There is no intrinsic incompatibility between network modelling and recognition of latent categories (Schweinberger & Snijders 2003), nor should there be any incompatibility between believing that some symptom clusters reflect latent classes *and* that symptoms within those clusters may have causal interrelationships. Measurement models may demand local independence (i.e., no association among symptoms after the latent variable is statistically controlled) and equal centrality of all symptoms, but these are limitations in their formalism, not a reason for dismissing the existence of latent variables in the domain of psychopathology.

The authors present a starkly dichotomous view of disorders. On the one hand, there are medical disorders such as Down syndrome that have discrete boundaries, essence-like etiologies, defining features, and isolated symptom clusters. The authors recognize that such disorders are latent categories, and symptom networks will therefore represent them incompletely. On the other hand are psychiatric disorders, which have "necessarily fuzzy" boundaries, diffuse etiologies, and no defining features. Their symptom clusters form densely interconnected webs that can be separated into distinct disorders only by arbitrary division. This view can be challenged because the distinction between essentialized natural kinds and arbitrary symptom clusters is too polarized, and because psychiatric disorders are not uniformly of the latter type.

Cramer et al. present psychiatric conditions as all alike in lacking sharp, non-arbitrary category boundaries. No doubt this is true of many disorders, which simply represent quantitative extremes on continuous dimensions. However, as I have argued elsewhere (Haslam 2002), mental disorders are structurally diverse. Many are differentiated from normality by an imposed and convention-based decision rule. Others have boundaries that are intrinsic rather than conventional, but those boundaries are themselves indistinct or fuzzy, representing gradations of abnormality. Still others are latent classes with discontinuous boundaries. The parameters of the category (e.g., its prevalence) are empirical matters that do not simply reflect where a *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) committee chose to set a diagnostic threshold.

The evidence that some mental disorders are latent categories comes largely from research using taxometric methods, which Paul Meehl and colleagues (Meehl 1995) developed to distinguish between (latently) categorical and dimensional models of psychiatric phenomena. The preponderance of taxometric findings support dimensional models of mental disorders, consistent with Cramer et al.'s view, but several latent categories have been found (e.g., autism, schizotypal personality; for a review, see Haslam 2003). It is implausible that these latent categories represent natural kinds in the essentialist sense – they may arise from threshold effects, complex interactions among multiple causal factors, and so on, rather than from a single underlying causal factor, or "specific etiology" – but they have non-arbitrary category boundaries and some kind of underlying causal process or mechanism that makes them coherent. The philosophical concept of "homeostatic property clusters" (Kornblith 1993), intended to strike a middle path between essentialism and conventionalism, is somewhat related. These clusters are "real divisions in the structure of the world" (Craver 2009, p. 577) that cohere not because they share an essence but through the operation of a similarity-generating mechanism. Demonstrating that some psychiatric disorders are taxonic in Meehl's sense does not commit one to essentialism, but it does invalidate any claim that all disorders are arbitrary and all boundaries fuzzy.

Taxometric research has direct relevance to questions of comorbidity (Meehl 2001; Waldman & Lilienfeld 2001). Comorbidity is meaningful as a concept only if the supposedly comorbid conditions are latent categories. Two disorders cannot truly co-occur in a person unless both are discrete and separable. If disorders are not taxa, then comorbidity merely represents overlap of symptoms from different diagnostic lists. Cramer et al. hold to this view of comorbidity, according to which it is primarily a nuisance to be eliminated by nosological revision. By excluding on principle the existence of latent psychiatric categories, they fail to acknowledge that some comorbidity may be real and meaningful.

I share Cramer et al.'s belief that most current psychiatric diagnoses do not pick out natural categories and that essentialist and reifying accounts of them should be vigorously challenged. For this reason, and because network analysis is a promising tool for mapping symptom space and reining in the promiscuous comorbidity of current diagnostic practice, I applaud their work. However, I hold a more pluralistic view of psychiatric classification than they do, believing that some psychiatric conditions approximate real categories with non-arbitrary and non-fuzzy boundaries. For this reason, I question the ontological position that they adopt, according to which all psychiatric boundaries are fuzzy, all distinctions arbitrary, and all comorbidity spurious. It should be possible to reap the benefits of network analysis without committing to a position that the symptom level is the only one that is real, and that latent categories could not occur within psychiatry.

Network models of psychopathology and comorbidity: Philosophical and pragmatic considerations

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Abstract: Cramer et al.'s account of comorbidity comes with a substantive philosophical view concerning the nature of psychological disorders. Although the network account is responsive to problems with extant approaches, it faces several practical and conceptual challenges of its own, especially in cases where the individual differences in network structures require the analysis of intra-individual time-series data.

Cramer et al.'s account of comorbidity is a thought-provoking contribution to the methodological foundations of psychopathology research. While we agree in spirit with the authors' motivations (e.g., addressing problems with latent variable approaches to comorbidity), we will point out several prima facie challenges for the network approach to comorbidity.

Consider the following philosophical views concerning psychological disorders. Realism, the view suggested by latent variable models, represents psychological disorders as the unobservable causes of symptoms. On this view, as Cramer et al. note, disorders exist independently of our measurement and diagnostic practices. They are detected through measurement. Conventionalist approaches, on the other hand, represent psychological disorders as artifacts of our measurement practices. For example, operationism collapses the distinction between disorders and their symptoms: the symptoms are constitutive of the disorders. Operationists define a disorder such as generalized anxiety disorder (GAD) as nothing more than the satisfying of a certain set of diagnostic criteria. As Cramer et al. note, the differences between these positions can have practical consequences such as different prevalence rates for a disorder. Cramer et al. have sought to carve out a third position with respect to comorbidity and psychological disorders. On their view, disorders are "clusters" of symptoms that systematically covary. Hence, it seems that on the network view, disorders do not exist independently of their symptoms. Disorders are aggregations of symptoms; this is very close to operationism. One logical consequence of this account is that psychological disorders cannot meaningfully be appealed to in causal explanations of pathological behavior. If GAD is just a specific cluster of symptoms, explaining why a patient manifests those symptoms by citing GAD would be circular.

Cramer et al. note that the network view agrees with many clinicians' conceptualizations of psychological disorders; however, there seem to be noteworthy ways in which the network view conflicts with clinical practice. Specifically, this view seems not to leave room for special cases, where clinicians would say that the psychiatric disorder is "latent" or "silent" (Lovett & Hood, in press). For instance, say that someone with schizophrenia experiences a lengthy period (several months) without symptoms. Does this person not have schizophrenia during that time? It is consistent with the latent variable approach to say that, for a time, the schizophrenia was not producing symptoms, but the network model does not seem to allow a representation of such a statement. To take a similar case, say that a child diagnosed with attention deficit hyperactivity disorder (ADHD) is placed in an environment where the behavioral symptoms are not permitted to be expressed; on the network view, has the ADHD been cured?

There are additional concerns about the practice of diagnosis itself under the network approach. *Individuals* are diagnosed with psychological disorders; however, symptom clusters in Cramer et al.'s models are determined by population-level data. It is well established that structures implied by covariation across individuals may not correctly represent cognitive structures in individuals (Borsboom 2005; Borsboom et al. 2009b; Hamaker et al. 2007; Molenaar 2004; Molenaar et al. 2003). This is the problem of *local homogeneity*, and it is a serious conceptual obstacle for realism with respect to latent variable models generally and psychometric models of intelligence, personality, and psychopathology in particular. As Cramer et al. note, this is a challenge for the network approach as well. They propose addressing it through the analysis of intra-individual time-series data (target article, sect. 8, para. 5), but there are conceptual and practical limitations to this approach. First, if intra-individual structures of covariation *in symptoms* vary across people, then each patient may have his or her own kinds of disorders, even if multiple patients share the same symptoms. In other words, in such a case, it would not be clear what the basis would be for saying two individuals have the same disorder. Second, suppose that this problem can be overcome and we have some criteria for issuing a diagnosis of, for example, delusional disorder. Cramer et al. would suggest that we diagnose a person as delusional on the basis of intra-individual time-series data. But such a diagnosis is then made relative to the patient's prior level of symptoms, and a patient who has long been consistently delusional would seem to be asymptomatic. Indeed, if a person with psychiatric symptoms seeks mental health services, and the mental health professional wishes to make a diagnosis, how long must the person's case be followed to note covariation in his or her different symptoms over time before a person-specific network structure can be developed and a disorder (defined as a cluster of symptoms) can be diagnosed?

These problems should be judged relative to the benefits of adopting a network approach. Certainly, the network approach can account for the relationships between symptoms that are not a product of common causes (i.e., violations of local independence), and it leads to an intuitive conception of disorders as having fuzzy boundaries. These virtues of the network approach are important conceptual benefits. However, the practical benefits claimed by Cramer et al. are less certain. For instance, Cramer et al. claim that symptom-symptom causal relationships are often the focus of clinical intervention. However, their examples on this point are not actually symptom-symptom relationships (unless "seeing a feared object is itself" a psychiatric symptom, as is "believing that one has not finished a list of tasks"); and in clinical practice, the symptoms themselves (and the consequent impairment in everyday life) are the focus of intervention rather than symptom-symptom relationships.

The challenges we raise here notwithstanding, Cramer et al.'s contribution is ambitious, and their proposal certainly warrants further consideration. We especially like how the authors endeavor to engage a wide audience of methodologists, clinical psychologists, and philosophers of science. In this they show the interdisciplinary relevance of comorbidity and the need to enlist the efforts of diverse specialists in addressing the nature of psychopathology and comorbidity.

Is there a contradiction between the network and latent variable perspectives?

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Abstract: First, we question whether Cramer et al.'s proposed network model can provide a viable scientific foundation for investigating comorbidity without invoking latent variables in some form. Second, the authors' claim that the network perspective is radically different from a latent variable perspective rests upon an undemonstrated premise. Without being demonstrated, we think the premise is potentially misleading.

Cramer et al. argue that we have been looking at mental disorders through the wrong psychometric lenses, and that we need a general psychometric theory of disorders as networks. Their article is valuable in as much as it raises the possibility of connecting psychometric theory to network models. However, we focus on two points of contention. Before doing so, we stress agreement on an overarching point: There is insufficient evidence that any mental disorder is a single continuous latent variable. As stated by Borsboom et al. (2004, p. 1063), the "ontological position that the attribute being measured exists and affects the outcome of the measurement procedure" is a strong scientific claim that is difficult, but necessary, to establish (see Michell 1999).

Having said that, our first point of contention is this: We do not think the authors convincingly argue that the network perspective "nullifies the need to invoke latent variables as an explanation of the covariance between symptoms" (sect. 1, para. 5). The authors recognize that "non-symptom causal processes" like homeostasis may mediate and "partly explain" relations between symptoms (sect. 2, para. 9). However, a network model needs to explicitly incorporate such causal mechanisms to form the basis of a scientific theory, and this would make causal mechanisms fundamental, not incidental. Thus, Holland (1998, p. 132) refers to mechanisms and their defining transition functions as the *primitives* of a network. In Kauffman's (1993) reaction network model of autocatalytic sets, for example, nodes may represent molecules, and edges may represent reactions: chemical reactions are the causal relations in the network. Without causal mechanisms, it is not clear how the network presented in the target article is anything *more* than a "method to visualize" sets of symptoms defined by the statistical associations in the empirical data (sect. 3). It would seem that, as soon as one invokes causal mechanisms, one must invoke latent variables like psychological and physiological states. Thus, we question whether the network perspective nullifies the need to invoke latent variables, in some form, to explain covariation among symptoms.

Our second point of contention is that Cramer et al. have not formally demonstrated the technical premise for claiming their network perspective is a radically different conceptualization to the latent variable perspective. The premise is that "the presence of direct causal relations between symptoms contradicts the essential assumptions that underlie psychology's main class of measurement models" (sect. 1, para. 5). This premise is asserted in the target article and references, but not formally demonstrated. Our concern is not whether the conceptualization is radically different. We are concerned that, without proper demonstration, the premise is potentially misleading.

Briefly, on a more basic issue, we think it worth making more explicit that latent variable models in Item Response Theory (IRT) *require* that *inter*-individual covariation between levels of a trait and item scores is "entirely attributable to the [latent variable]" (sect. 2, para. 3). We assume, then, that the authors' premise pertains specifically to *intra*-individual processes, given that in a source cited in the article, Borsboom (2008, p. 1101) questions whether symptoms are effects of a common cause "at the level of the individual person." In asserting their premise, the authors focus specifically on the assumption of *local independence*. Borsboom (2008) uses the analogy of temperature to explain local independence, likening the reading of thermometers to indicators of latent variables. For a fixed temperature, there is no covariation among the readings. Borsboom (2008, p. 1099) says "the same implication exists in latent variable models, where this property is called local independence ('local' in the sense that one position on the attribute is considered at a time, and 'independence' because the indicators are statistically independent in the subpopulation of people who occupy this position)." As Borsboom explicitly states, this is an *implication* of local independence: See Lord and Novick (1968, p. 361) for a formal *definition*.

Expressed in these terms, the implication is that for a subpopulation at a single position there should be no inter-individual covariation among item responses. However, to argue that this lack of covariation precludes causality would be to risk arguing by selective observation. The reason is that IRT models require that an individual's responses to items are correlated with the locations of the *items* on the latent variable. One of the pioneers of IRT, Rasch, explained this implication of his dichotomous IRT model by showing there were positive correlations between item estimates and the log-odds of correct responses to the items, for groups of respondents with similar raw scores (see Rasch 1960/1980, Figure 7, p. 89). He treated the raw score groups as relatively homogeneous with respect to the latent variable. Thus, even at the level of the individual, local independence does not preclude covariation, attributable to a latent variable, among responses. One cannot, therefore, argue that local independence precludes causation at the level of the individual on the basis that no such covariation may exist. Whether there is a plausible scientific basis for proposing that one or more latent variables cause the relations among indicators is a separate matter, which is justifiably raised in the target article and references. However, it would be unfortunate if readers are led to believe that local independence necessarily means one cannot apply existing psychometric theory if it is posited that intra-individual relations among symptoms are due to a latent variable.

Moreover, a body of work in IRT focuses on polytomous models for items with explicitly dependent categories, such as categories that form a rating scale. These models accommodate direct *dependence* between the response categories that would otherwise violate the assumption of local independence (Andrich 1985; 2005; Verhelst & Verstralen 2008). It may be possible to develop methods to apply these models where there are direct causal relations among symptoms.

In summary, first, we contest that the network perspective proposed by Cramer et al. nullifies the need to invoke latent variables. Second, we argue for the need to thoroughly examine whether existing models can be applied before calling for a new "general psychometric theory" (sect. 8, para. 9).

Network origins of anxiety and depression

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Abstract: Cramer et al. contrast two possible explanations for psychological symptoms: latent variables (i.e., specific cause) versus a network of causality between symptoms. There is a third explanation: The reason for comorbidity and the reported network structure of psychological symptoms is that the underlying biological cause is a psychoneuroimmunoendocrine information network which, when dysregulated, leads to several maladaptive psychological and somatic symptoms.

It is entirely plausible that symptoms should have a direct causal relationship with one another and this relationship has a network structure. It is implausible that symptoms arise *only* from mutual causality. They cannot arise out of thin air. This commentary addresses the origins of anxiety and depression.

Modern Western medicine is based on an untested assumption of specificity: each disease has its own unique pathophysiology. The biological explanation of depression and anxiety is consistent with this assumption. A multi-billion dollar pharmaceutical industry stems from the hypothesis that depression results from low levels of serotonin, and anxiety from low levels of gamma-aminobutyric acid (GABA). According to this hypothesis, the "latent variables" referred to by Cramer et al. are not really latent (i.e., hidden) – they are known neurotransmitters. If only life were that simple. Not only is the serotonin hypothesis widely disputed (Lacasse & Leo 2005), but drugs which enhance serotonin have a marginal effect on depression as the effectiveness of these drugs is largely placebo mediated (Kirsch 2009). If the unique neurotransmitter explanations for depression and anxiety are an over-simplification, what is causing these symptoms?

According to infornet theory (Hyland, in press), the body is organised in two ways: (a) as a sequential processing system

that leads to specific pathologies and the diseases associated with those specific pathologies, and (b) as a parallel processing system. The parallel processing system extends through the neural, immune, and endocrine systems; it is a psychoneuroimmunoendocrine information network system, or *infornet* for short. The infornet carries out a number of functions, including managing the reference criteria of homeodynamic control systems. Reference criteria of homeostatic control systems remain fixed; those of homeodynamic systems vary and are responsive to both internal and external events.

The infornet integrates information from external or psychological inputs with information from internal or biological inputs. Outputs from the infornet to the cortex generate mental states that modify behaviour and hence modify the external environment. For example, pain is a signal that leads to adaptive behaviour – such as, withdrawal of one's hand from a flame. According to infornet theory, anxiety and depression evolved as signals to modify behaviour. Anxiety is a signal of behavioural alarm and prepares the body for external danger. Depression is a signal of behavioural inhibition and is the consequence of behavioural patterns that fail to achieve a person's important goals (Hyland 1985). Depression helps disengage behaviour from unattainable or inappropriate goals (Carver & Scheier 1990). Anxiety and depression are therefore caused by outputs from a parallel processing system involving many different biochemicals, rather than being directly caused by a single biochemical.

Because it encodes meaning, the infornet can be described in terms of the meaning it contains – by analogy, a computer programme can be described in terms of what it does rather than a binary magnetic code. The meaning of the infornet is represented by infornet beliefs. Infornet beliefs create the instructions that alter the reference criteria of homeodynamic control loops and which provide the mental signals that alter behaviour.

The infornet beliefs that lead to anxiety can be characterised as "the external environment is dangerous." The infornet beliefs that lead to depression can be characterised as "I am not achieving the goals I want to achieve" (Carver & Scheier 1990; Hyland 1987). Beliefs tend to be interconnected and mutually supporting. The infornet beliefs leading to depression and anxiety are interconnected via a network structure of linked beliefs. Both of these mood-altering infornet beliefs are part of a more general belief that "the external environment is unsatisfactory," and this more general belief is part of a top-level belief that "the general situation is bad." If the general situation is bad, then not only is there threat from the external environment but also threat to the internal environment (e.g., threat of infection or damage). Consequently, the top-level belief of "the general situation is bad" is also associated with beliefs that drive the inflammatory response system (Rosenkranz 2007; Segerstrom & Miller 2004). Infornet dysregulation occurs when, through the application of network learning rules that normally create better self-regulation, the infornet develops maladaptive beliefs – for example, that the general situation is always very bad when it is not. Chronic depression and anxiety (i.e., mental states which cannot be attributed to the immediate situation) are signals of a dysregulated infornet; that is, an inappropriate response to the current situation. Correlations between depression and anxiety, on the one hand, and between depression, anxiety, and inflammatory mediators, on the other, arise because all these variables are outputs of an information system whose beliefs are interconnected and where maladaptive beliefs tend to spread.

Why do Cramer et al. observe a network structure in the relation to psychological symptomatology? My guess is that causality between symptoms plays a minor role. I suggest that the main the reason for the network structure of symptom comorbidity is because of an underlying biological network structure. That is, anxiety and depression are outputs from a dysregulated infornet that has multiple physiological and psychological outputs.

Infornet theory predicts that fuzzy boundaries between disease states will not be limited to psychological symptoms but will include somatic symptoms. Diseases without a specific pathology, such as chronic fatigue syndrome (CFS) and irritable bowel syndrome (IBS), have a variety of psychological and somatic symptoms: diagnosis is not based on a unique pattern of symptoms. Comorbid relationships between fatigue, the somatic symptoms associated with CFS and IBS, along with depression and anxiety, should all form part of a network structure. In particular, inflammatory somatic symptoms should be related to psychological symptomatology (Whalley 2007). Dysregulated people have multiple and varied symptoms. Dysregulation varies continuously across the infornet's meaning space.

If diseases have a specific cause, then comorbidity is an inconvenience. Comorbidity is often a reason for exclusion in clinical trials. From the perspective of infornet theory, however, the study of comorbidity has the potential to provide unique insights into a hypothesised network system whose outputs are psychological symptoms along with physiological changes (typically, pro-inflammatory) that cause somatic symptoms.

The network perspective will help, but is comorbidity the question?

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Abstract: Latent variable modeling has revealed important conundrums in the *DSM* classification system. We agree that the network perspective has potential to inspire new insights and resolve some of these conundrums. We note, however, that alone it cannot really help us understand etiology. Etiology, not comorbidity, is the fundamental question.

It has become popular in the last few years to model large sets of inter-correlated variables as networks. There are probably two reasons for this. First, and perhaps trivially, as was the case about 25 years ago with latent variable modeling, the statistical techniques and tools to do this network modeling tractably and readily are relatively recently available; that is, researchers now can. This is, however, not a priori a reason to take whatever it offers us as the best answer to our scientific questions (Gigerenzer 1991). But second, again as did latent variable modeling about 25 years ago, the network perspective offers exciting prospects for fresh understanding of dynamic systems ranging from power grids, to epidemic spread through a population, to the development of chronic disease such as diabetes in individuals. Psychopathology, with its common occurrence and multifaceted manifestations seems a particularly apt target for the network perspective, and we are pleased to see Cramer et al. take some concrete steps towards applying it.

At this point, problems with the *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders, 4th edition*) system of psychopathological diagnostic system are widely acknowledged. Despite Cramer et al.'s criticism of it, much of the credit for revealing those problems, perhaps especially comorbidity, should rest with latent variable modeling (e.g., Krueger et al. 2007). Latent variable modeling might also be credited with something else: revealing the tension between trying to use the same diagnostic system for purposes of systems of administration

and treatment and for purposes of understanding development and etiology. The former takes place and requires description at the level of the population, whereas the latter takes place and requires description at the level of the individual. Researchers can count on latent variable modeling to tell us something about the former, but whatever it says may not apply to the latter (e.g., Cervone 2005; Molenaar 2004).

As Cramer et al. note, the reason latent variable modeling may not tell us about development and etiology involves the assumption of local independence underlying it. From the latent variable perspective, pervasive comorbidity is the chronic symptom of this trouble. If two disorders share the same symptom, how can there be local independence of symptoms? And if two disorders share the same symptom, it should be no surprise to find comorbidity. But it is the strong causal attributions of latent variable models that carry with them the need for assumptions like local independence, not the structural equations that define the parameters to be estimated themselves. The appropriateness of latent variable models is assessed by how well those structural equations can replicate the data, not by any direct test of the appropriateness of the causal attributions. Completely different patterns of causal attribution can be described by the same sets of structural equations, and these different causal models will fit the data equivalently. For example, it is probably just as likely that depression emerges from a constellation of symptoms as it is that depression is the underlying latent cause of those symptoms, and the two models would fit the data identically well (Borsboom et al. 2003). If depression does emerge in this way from a constellation of symptoms, the co-emergence of some other disorder that shares those symptoms is no problem at all, as, for example, when obesity contributes to the emergence of both heart disease and diabetes. Thus, comorbidity is a problem not because of the structural models that have been used but because of the causal attributions associated with latent variables. Administration systems rely on accurate description and need not rely on causal understanding at all. In fact, many of the most effective treatment protocols to date have not relied on causal understanding. But ultimately understanding psychopathology will rely critically on understanding development and etiology. For that, researchers only get in trouble when they assume what they should be trying to test. Thus, the critical problem with latent variable models is not really the comorbidity they have helped to identify, but the causal attributions they entail.

Cramer et al. have demonstrated that the network perspective offers potential to develop important insights into the patterns of association among *DSM-IV* symptoms, particularly through the possibilities it offers to include estimates of parameters that express the relative frequencies of nodes and the extent to which they are interconnected with other nodes. More importantly, even when the causal assumptions in latent variable modeling are relaxed, their structural models can be accurate descriptions at the level of the population, but may not be accurate at the level of the individual, which is of necessity also the level at which function must be understood. Network models cannot guarantee consistency between the intra- and inter-individual levels either, but they may be more likely to show it, though this remains to be tested. It might also turn out that a combination of transactional processes (as can be modeled in networks) and latent causal factors provides the best description of the development of some traits (Fraley & Roberts 2005). Perhaps most important of all, however, the use of new statistical tools such as network modeling frees us to think about etiology in new ways. Network models cannot tell us directly about causation either, especially if we are not even sure that we have the optimal symptom designations for the disorders, as Cramer et al. hint and we would emphasize. Nor can they help us fix the *DSM* if we do not have the optimal symptom designations. But they can open our minds to new ideas about etiology that can be tested in other ways, especially if we go beyond the basic cross-sectional data Cramer et al. have used for illustration here. And that's what we need to be thinking about.

Toward scientifically useful quantitative models of psychopathology: The importance of a comparative approach

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Abstract: Cramer et al. articulate a novel perspective on comorbidity. However, their network models must be compared with more parsimonious latent variable models before conclusions can be drawn about network models as plausible accounts of comorbidity. Latent variable models have proven generative in studying psychopathology and its external correlates, and we doubt network models will prove as useful for psychopathology research.

In the target article, Cramer et al. offer a novel psychometric perspective on symptoms of major depression, generalized anxiety disorder, and patterns of co-occurrence among these symptoms. The study of human individual differences has always benefited from its close relationship with psychometric theory and models, and the application of psychometric models in the study of psychopathology provides a much-needed remedy to assuming that the constructs delineated in the *DSM-IV-TR* (*Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision*; American Psychiatric Association 2000) are valid by fiat (Krueger & Markon 2006a).

The ultimate utility of the work of Cramer et al. in understanding and ameliorating psychopathology, however, hinges on evaluating the *comparative construct validity* of their approach. Network models are only one type of model, and Cramer et al. do not compare the fit of their models with the fit of other plausible models. Importantly, Cramer et al. do not directly compare network and latent variable models. Indeed, these comparisons may be moot in some cases, as network and latent variable models may be more similar than Cramer et al. suggest. We expand on these points here.

Comparative construct validity of quantitative models of psychopathology. A fundamental limitation of the work presented by Cramer et al. pertains to their selective approach to model fitting. They present the results of fitting network models, but not the results of fitting other psychometric models. Their strategy is instead to argue on an a priori basis that other models (e.g., latent variable models) should not be considered as potential models.

This strategy is obviously problematic. The selection of a quantitative model is an empirical matter, not a matter that can be decided a priori. As Cramer et al. point out (e.g., in their use of the Akaike Information Criterion [AIC] as an index of fit; sect. 2, para. 8), a desirable model can be thought of as balancing at least two properties: (1) the ability to reproduce the observed data and (2) the efficiency or parsimony with which the model can achieve the first property, more efficient models having greater scientific utility if they are equivalent in their ability to reproduce the observed data (Markon & Krueger 2004).

With regard to model fit, the network models proposed by Cramer et al. are unlikely to emerge as optimal models when

compared with latent variable models. This is because the network models fit by Cramer et al. contain a multitude of parameters; they are lacking in parsimony when compared with latent variable models. Models lacking in parsimony often provide a poor relative fit to data and are thereby lower in scientific utility because they amount to little more than re-expressions of observed data (Barron & Cover 1991). Because they capitalize on chance, they also tend to generalize poorly to new samples of measures or persons. Heavily parameterized models lack the ability to articulate organizing scientific constructs that have proven indispensable in building theories and evaluating the correspondence between theories and data.

Consider, for example, the model shown in Cramer et al.'s Figure 4, portraying network-model derived connections among the symptoms of major depression and generalized anxiety disorder. Cramer et al. attempt to argue that the multiplicity of parameters portrayed in Figure 4 (the size of the nodes, the darkness of the circumferences, the thickness of the edges, and the darkness of the edges) provides valuable information in focusing scientific inquiry aimed at understanding and ameliorating depression and anxiety. However, the fit of this highly complex model is never compared with other models that articulate organizing scientific constructs (i.e., latent variable models). By virtue of their greater parsimony and articulation of organizing constructs (e.g., the latent construct of neuroticism as the nexus of anxiety and depression; Griffith et al., in press), latent variable models point us toward key targets for scientific inquiry.

Such guidance is obviously critical in pursuing research aimed at reducing the public health burden of mental disorder (Lahey 2009). Put simply, how would one use the information in Figure 4 to explain to a policy maker how we might go about spending public funds wisely in the service of working to ameliorate the burden of depression and anxiety? By funding hundreds of separate projects focused on understanding each line in the figure? We doubt such a conversation would prove generative, or that scientific inquiry framed by Figure 4 would prove enlightening. We would also encourage the reader to contemplate how complicated Figure 4 would look if a more comprehensive set of psychopathological symptoms (e.g., symptoms of other mood and anxiety disorders) were modeled along with the specific symptoms that were the focus of Cramer et al.'s efforts.

Although comparative models of internal structure are an important step in model development, a next step is to evaluate the ability of a model to explain external constructs. Space considerations prevent us from describing the extensive literature on the construct validity of latent variable models of psychopathology at length. We can provide only a few examples but encourage the reader to consult the citations we give for more details. As examples, latent variable models of psychopathology can account for phenomena such as gender differences in the prevalence of specific syndromes (Kramer et al. 2008), the genetic and environmental effects that both connect and distinguish specific syndromes (Kendler et al. 2003), and the generality and specificity of biobehavioral correlates of psychopathology (Patrick et al. 2006).

Ultimately, some comparisons between network models and latent variable models may be moot, because the two frameworks are more similar than Cramer et al. suggest and may be identical in many cases. Importantly, network models of the sort espoused by Cramer et al. would be latent variable models if they included multiple measures of each symptom, rendering each of their nodes a latent variable. Thus, latent variable models are not only more parsimonious, but also more comprehensive than the models discussed by Cramer et al. Moreover, some sophisticated network models have proposed constructs very similar to latent variables (Kemp & Tenenbaum 2008). Theoretical discussions about the relative merits of latent variable versus network models are fundamentally misleading. The important questions are what models to compare empirically, how to make those comparisons, and what those empirical comparisons reveal.

Questions about networks, measurement, and causation

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Abstract: Cramer et al. present a thoughtful application of network analysis to symptoms, but certain questions remain open. These questions involve the intended causal interpretation, the critique of latent variables, individual variation in causal networks, Borsboom's idea of networks as measurement models, and how well the data support the stability of the network results.

I wish to congratulate Cramer et al. for writing an audacious article that offers much food for thought. Among other things, the target article provides a welcome expansion on ideas presented by Borsboom (2008). I focus on areas that could use further fleshing out and on psychometric and methodological issues, leaving clinical issues for others with expertise in that area.

The causal interpretation of the network models puzzles me most. Cramer et al. state a tentative causal interpretation as: "the stronger the association between symptoms, the more likely that one symptom will lead to another" (sect. 6, para. 11); but the article does not develop the causal interpretation and instead focuses on modeling symmetric associations. If the authors intend a symmetric notion of causation, this seems like a very strong restriction on the models that rules out cases such as Borsboom's (2008) chain model in which panic attacks cause concern, but not vice versa. Asymmetric causation brings us back to something akin to a path diagram, although the positing of nonlinear causal connections by using a threshold parameter would add an interesting additional element to the causal model. However, even asymmetric bidirectional causal models face conceptual hurdles (Rozeboom 2009). Certainly one needs to conceptually distinguish causal parameters from associations (McDonald 2002), even if one then intends to argue in favor of equating them. A good deal of work remains to clarify various possible causal interpretations and evaluate their relative merits.

A second aspect of the article that I found difficult involved the critique of latent variable models. Cramer et al. make a reasonable case against a single common factor for all symptoms listed for a disorder in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*). However, a critical latent variable modeler would inspect the symptom correlation matrix showing the same patterns of association described in the network, warning against a single common factor, or catch the problems when assessing model fit. As a result, much of the critique of latent variable models seems tilted in favor of networks by making a mismatched comparison of a proper network model against an improper latent variable model. Perhaps improper use of latent variable models occurs in the diagnostic literature, but then the criticism applies to the misuse of such models, not the models themselves.

The advocacy against latent variable models risks becoming an advocacy in favor of analyzing causal relationships between observed variables rather than latent variables, and this holds several potential pitfalls. One motivation for using latent variable models involves the ability to remove the attenuating effects of measurement error from the estimates of causal relationships. Replacing latent variable models with causal networks of observed variables negates this advantage. As a thought experiment, imagine modeling a network of variables measured without any error. Now imagine a knob that allows you to gradually turn up the amount of random measurement error mixed into the observed variables. As you turn the knob, you can expect the estimated causal connections between the nodes to decrease, eventually to the point that alternative networks become increasingly indistinguishable based on the observed data.

An alternative would involve developing multiple measures of each symptom. One could then treat each symptom as a latent variable with its own common factor model, and model the causal relationships between symptoms as relationships between these latent variables (Bollen 1989). This would allow the research to both control for measurement error and model direct causal relationships between the symptoms. As such, it remains unclear that shifting the focus to causal relationships between symptoms requires giving up measurement models and their advantages, but these two issues seem conflated in Cramer et al.'s article. I see no motivation for encouraging a return to observed regularities as the primary object of scientific explanation.

Cramer et al.'s comments regarding different causal networks for different individuals seem to cut against the presented network analyses and in favor of a return to some kind of latent variable model. Latent class analysis, or latent mixture modeling, provides a means of identifying stable subclasses of individuals sharing the same causal structure. Cramer et al. sensibly suggest modeling individual differences on the network parameters, allowing each individual his or her own causal structure. However, if clusters of individuals share the same causal structure, the latent mixture would provide a more parsimonious model than one that states that everybody differs from everybody else.

Borsboom (2008) suggested understanding symptoms as parts of disorders but took this as an alternative measurement model. Cramer et al. definitively reject the idea that symptoms measure disorders. I did not find the motivation for this shift clear from Cramer et al.'s presentation and would like to see further work fleshing out Borsboom's original idea that symptoms can both constitute and measure a disorder, or at least that symptom severity can measure disorder severity despite this constitutive part-whole relationship.

A final minor point involves the use of random split-sample cross-validation to support conclusions regarding the stability of the results of the network analyses. It seems unsurprising that a random split of such a large sample would produce the same results in each half, but it remains unclear why this provides support for the stability of the results. Resolving the issue requires greater clarity regarding the intended notion of stability. However, a more informative approach might instead make use of the methods outlined by Shadish et al. (2002) for systematically examining the consistency of the results across various possible moderating variables available in the data set. Such non-random stratification of the sample might provide a much more informative and stringent assessment of the stability of the results.

Again, I wish to congratulate Cramer et al. for having written such a far-reaching article. I hope that my comments can play a constructive role in moving the research program forward and look forward to further developments.

Symptoms as latent variables

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Abstract: In the target article, Cramer et al. suggest that diagnostic classification is improved by modeling the relationship between manifest variables (i.e., symptoms) rather than modeling unobservable latent variables (i.e., diagnostic categories such as Generalized Anxiety Disorder). This commentary discusses whether symptoms represent manifest or latent variables and the implications of this distinction for diagnosis and treatment.

Cramer et al. model behavioral disorders purportedly using manifest variables (symptoms) rather than latent constructs (diagnostic categories). We challenge the assumption that a symptom is a manifest variable, and use the symptom of sleep disturbance as an example because the target article authors have used this as an exemplar of a symptom shared by several disorders (cf. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*; American Psychiatric Association [APA] 1994). It might seem that a symptom such as sleep disturbance is an empirical observation rather than a theoretical abstraction like depression; but sleep disturbance is itself an abstraction that encompasses multiple, specific instances of sleep loss: delayed sleep onset, mid-sleep and early morning awakening, restless sleep, and disturbed circadian rhythms and sleep stages (APA 1994). To say that someone has a sleep disturbance is to assert that they are disposed to have multiple instances of sleep loss in one or more of these domains.

Conceptualizing symptoms as manifest or latent variables has implications for assessment. The nodes in Cramer et al.'s network were categorically defined symptoms assessed with the Composite International Diagnostic Interview (CIDI) (Kessler & Uslum 2004; Kessler et al. 2005b), a structured clinical interview in which symptoms are assessed in terms of presence/absence rather than with a dimensional score. Clinical interview is one among several methods of assessing sleep disturbance, including questionnaires, diaries, polysomnography (PSG), and laboratory observations, each of which differs in their reliability and validity (Crocker & Algina 1986). Reliability considers the similarity between observed and true scores. It is necessary to make this distinction if one assumes that the same phenomenon is being measured during multiple observations. In the case of validity, a distinction is made between what is being measured and the instrument that is used to measure it. For example, we might assume that an interview and PSG measure the construct of sleep disturbance, though they might differ in their validity (i.e., the extent to which they are influenced by other factors). Moreover, there is an implicit understanding that the true sleep disturbance score represents a latent variable composed of the observations (manifest variables) of each testing occasion. Hence, the categorical sleep disturbance symptom assessed by the CIDI is assumed to be an abstraction of manifest (observed) instances of sleep loss.

Conceptualizing symptoms as latent constructs has implications for diagnostic validity.

What is the nature of the categorically defined symptom of sleep disturbance as a unit of analysis in diagnostic classification and differential diagnoses of mood and anxiety disorders? The determination that sleep disturbance is a symptom of a mood or anxiety disorder assumes the following: the sleep loss is frequent, substantial, persistent, unintentional; not due to the presence of a medical condition or a substance; and not due to extrinsic (environmental) factors (APA 1994). Insomnia complaints are common in the population, with a one-year prevalence of 30–40% (APA 1994). Hence, ascertaining the frequency, intensity, and persistence of the sleep disturbance is necessary to assess whether it is severe enough to be considered abnormal. Intentional sleep loss (e.g., a student who remains awake all night studying for exams), or sleep loss due to a medical condition, use of substances, disrupted circadian rhythms (e.g., jet lag), or due to environmental factors (loud neighbors), would not be diagnosed as a symptom of a mood or anxiety disorder (APA 1994). We therefore contend that sleep disturbance as a symptom of a mood or anxiety disorder is a latent construct that encompasses manifest observations of unintentional, frequent, substantial, and persistent sleep loss not due to the aforementioned extrinsic factors, and that these manifest variables must be assessed in order to determine whether the sleep disturbance does in fact qualify as a bona fide symptom of a mood or anxiety disorder.

Consider the symptom of sleep disturbance in posttraumatic stress disorder (PTSD). Though this PTSD symptom has many features in common with primary insomnia (e.g., Inman et al. 1990), sleep disturbance in PTSD can be discriminated from that in primary insomnia according to differences in REM-sleep abnormalities (e.g., Inman et al. 1990; Mellman et al. 2002) and frequency of sleep disturbance due to nightmares (Mellman & Pigeon 2005), due to fear of sleep and of the dark (Inman et al. 1990), or due to nocturnal hypervigilance (e.g., lying awake listening for strange sounds) (Deviva et al. 2005). Hence, although the construct of sleep disturbance is found in several behavioral disorders (APA 1994), the observed manifestations of sleep disturbance in PTSD can be discriminated from those associated with other behavioral health conditions. Analysis of sleep disturbance as a latent construct reflecting manifest observations such as, for example, frequency of delayed onset due to fear of nightmares could reduce diagnostic overlap and enhance diagnostic validity. Clinical scientists have also recognized the distinction between sleep disturbances in PTSD and those found in other disorders by developing interventions for PTSD patients that specifically target nightmares and nocturnal hypervigilance (Deviva et al. 2005). Hence, recognizing that a symptom reflects a latent construct is not an abstract, semantic issue. Regardless of whether one adopts network or latent construct models of behavioral disorders, a clear understanding of how we define and measure behavioral phenomena, and of the nature of the units of analyses we employ to characterize disorders, has nontrivial implications for determining the best course of treatment, which is the ultimate goal of developing accurate diagnostic methods.

Treating symptoms as proxies for manifest observations leads one to think of them as empirical observations rather than as theoretical constructs. However, assessment, diagnosis, and treatment of behavioral disorders are better served by careful consideration of the basis on which symptoms are identified and measured.

Latent variable models are network models

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Abstract: Cramer et al. present an original and interesting network perspective on comorbidity and contrast this perspective with a more traditional interpretation of comorbidity in terms of latent variable theory. My commentary focuses on the relationship between the two perspectives; that is, it aims to qualify the presumed contrast between interpretations in terms of networks and latent variables.

All models with common latent variables (factors) can be transformed into equivalent network models without common latent variables. This was proven in Molenaar (2003); Molenaar et al. (2007) apply this transformation to the 1-factor model. The networks that are equivalent to latent variable models are directed graphs connecting observed variables and residuals. In contrast, the networks in the target article are undirected graphs connecting observed variables (symptoms). Notwithstanding these differences in detail, the fact that any latent variable model can be transformed into an equivalent network model (where *equivalent* means the same number of free parameters and goodness of fit to the data) implies that latent variable models can be conceived of as constituting a subset of the set of network models. This, of course, qualifies any presumed contrast between interpretations in terms of networks and latent variables.

The transformation of models with common latent variables into equivalent network models without common latent variables is akin to the transformation of linear state space models into equivalent transfer function models, which is standard practice in computational engineering and signal analysis. A typical state space model is composed of two sub-models: a measurement model linking the observed process to the latent state process, and a dynamic model describing the evolution of the latent state process. In contrast, a transfer function model consists of time-lagged relationships involving only the observed process and residuals. Again, it holds that state space models constitute a subset of the set of transfer function models.

State space models are very popular in applied dynamic systems analysis. Dynamic systems theory is discussed in the concluding section of the target article. Linear state space models are formally equivalent to longitudinal factor models, the latter being typical instances of psychometric latent variable models. Hence, in so far as the authors see an important role for dynamic systems theory within a network perspective, there also should be a role for state space models and longitudinal factor models.

The model equivalences sketched here are suggestive of a rather gradual relationship between network models and latent variable models. The networks presented in the target article are undirected graphs in which the edges reflect associations between observed variables. The analogue for multivariate Gaussian variables would be a covariance matrix depicted as a graph. Such graphs, often augmented by colorings conveying additional information, certainly constitute important tools to display observed relationships among a large number of observed variables. But displays of relationships among observed variables, whether in graphical network form or as arrays of covariances, constitute a low level of modeling. An intermediate level of modeling would include path analysis or transfer function modeling; that is, models involving networks of directed connections among observed variables and residuals. At this level the effects of measurement errors can be taken into account, which appear to be quite important in social-scientific measurements. An example is the generalization of the simplex model to the quasi-simplex model. The highest level includes state space models and psychometric latent variable models. These models explain observed relationships in terms of common causes and measurement error and therefore are ideal for scientific theory formation. They are not as restricted as mentioned in the target article. For instance, measurement errors in state space models can be sequentially dependent and/or can depend upon the latent state process. But obviously they put the strongest demands on the data.

Cramer et al. are correct in stating that not every set of observed variables can be explained in terms of a limited number of common causes, despite the heuristic and scientific value of such an explanation. For instance, with respect to the networks presented in the target article this would explain what the symptoms are symptoms of. Therefore, one would like to have available a set of adequate inductive tools to determine whether or not each symptom (node in a network) has its own etiology. Or, stated more generally, one would like to have adequate inductive tools to progress from the lowest level of modeling (displaying networks of relationships among observed variables) to higher levels.

Some mental disorders are based on networks, others on latent variables

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Abstract: Cramer et al. persuasively conceptualize major depressive disorder (MDD) and generalized anxiety disorder (GAD) as network disorders, rejecting latent variable accounts. But how does their radical picture generalize across the suite of mental and personality disorders? Addictions are Axis I disorders that may be better characterized by latent variables. Their comorbidity relationships could be captured by inserting them as nodes in a super-network of Axis I conditions.

The network perspective on major depressive disorder (MDD) and generalized anxiety disorder (GAD) articulated by Cramer et al. in the target article captures a good deal of the scientific data on, and clinical experience with, those most ubiquitous and protean of Axis I disorders (cf. *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (*DSM-IV*) for definitions of Axis I; American Psychiatric Association 1994). MDD and GAD are not only strongly comorbid with one another, but with a wide range of psychiatric afflictions. It is highly plausible that they designate the most common clusters in the network of co-occurring symptoms of serious mental distress generally. Equally worthy of further study and development is the authors' suggestion that the causal relationships among these symptoms are typically directly mediated, in part, by external factors (perhaps including the communication of psychiatric diagnoses to patients, a potential "etiological node" [sect. 4, para. 5] that Cramer et al. don't mention). It is this aspect of the network perspective that renders it a radical and welcome challenge to standard latent variable models. The authors are also importantly right in identifying the implicit commitments of such models with the psychometric methods used in their application, rather than with associated philosophical rhetoric.

Cramer et al. are not explicit about the way in which they expect their radical picture to generalize across the suite of mental and personality disorders. We may distinguish two possible interpretations that are compatible with their remarks. On the one hand, it might be that the network model applies to most disorders directly, just as it does to MDD and GAD. On this interpretation, most disorders are clusters of nodes in a single super-network of psychiatric conditions. Alternatively, the network structure of MDD and GAD, along with the ubiquity of their constitutive symptoms, might explain comorbidities involving other Axis I and Axis II disorders which are themselves based on latent variables. Evidently, the second "hybrid" picture would be more complicated and inelegant. However, I believe that the limited current evidence runs more strongly in its favor.

A major class of Axis I disorders that seems most likely to demand this hybrid conception is that of the addictions. As is distinctly *not* true of MDD or GAD, recent progress in understanding addiction has consisted mainly in progressive isolation and refinement of a neural pathways model of its etiology and maintenance (Everitt & Robbins 2005; Everitt et al. 2001; Goldstein & Volkow 2002; Koob 2006; Koob & LeMoal 2000). Summarizing very broadly, it seems to have been discovered that addiction arises through the dopamine reward circuit's learning a rich but entrenched set of cues that activate representation of highly valued and strongly salient addictive targets and that prepare motor response to consume them, which, when frustrated, are experienced as cravings. A crucial step in the etiology of addiction appears to be adaptation of frontal and prefrontal serotonin and gamma-aminobutyric acid (GABA) circuits that weakens the strength of opponent processes to impulsive consumption.

If learned reward system hysteresis and neuroadaptation that weakens cortical control are taken to be jointly necessary and sufficient conditions for addiction, then many people who consume addictive substances, or gamble, to problematic levels are probably not addicted. "Problem drinking" and "problem gambling" are very plausibly behavioral syndromes with network structures. However, what would precisely distinguish true addicts, according to the perspective being suggested, are specific ranges of values for neural processing variables in the anterior cingulate, ventral tegmental area (VTA), the ventral striatum including nucleus accumbens, and the orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (PFC). Preliminary evidence for this view comes from the first taxometric analyses of mixed populations of substance-abusing and substance-dependent people. Goedeker and Tiffany (2008) find strong convergence among three taxometric methods in identifying a taxon of heavy daily cigarette smokers, who also meet traditional clinical criteria for dependence, that excludes the large group of less regular nicotine users. That is, nicotine dependence does not appear to have a dimensional structure, in strong contrast to the findings of the same taxometric approaches as applied to analogue depression (Ruscio & Ruscio 2002) and attention-deficit hyperactivity disorder (ADHD) (Haslam et al. 2006).

A disorder's being characterized by a network model does not entail that, under the guise of a latent variable perspective, its structure should emerge as dimensional. Nor does the inverse dependence hold: from the fact that a disorder's latent structure suggests a taxon one cannot infer rejection of a network model. However, Cramer et al. identify the view opposed to the network perspective as "essentialism" (sect. 6, para. 7), which in the case of mental disorders is the idea that people can be separated into *disorder* and *no disorder* classes on the basis of presence or absence of specific "defining features" (sect. 6, para. 1). In the case of addiction, such defining features which are *not symptoms* have been proposed on the basis of neuroscientific evidence; in this context, confirmation of taxonic structure buttresses the hypothesis that the features in question are indeed defining – that is, that addiction resembles Down's syndrome, Cramer et al.'s example of a medical condition that is not based on a network. It might thus be suggested that Cramer et al. overstate what the evidence will bear when they say baldly that "this line of reasoning [applied to Down's syndrome] is unlikely to hold for mental disorders" (sect. 6, para. 2). On the other hand, the issue might be thought to turn partly on semantics: someone might want to maintain that if addiction is a distinctive, identifiable pathology of the VTA-to-PFC/OFC circuit, then it is not really a mental disorder after all.

Addictions are highly comorbid with other Axis I and Axis II disorders, including MDD, ADHD, bipolar spectrum disorder, and antisocial personality disorder. A possible way of representing this is to conceive of addictions, themselves modeled using latent variable structures, as nodes in the overarching network of mental disorders. On this representation, however, comorbidities *among* addictions would not be best modeled by network analysis. Comorbidity among addictions might be grounded etiologically in a genetic predisposition, and manifestly in the common attenuation of cortical control circuits in addicts.

Cramer et al. have supplied a promising and liberating way of thinking about psychiatric comorbidity. They likely would not want to be taken as suggesting that it is the whole story.

Comorbidity: The case of developmental psychopathology

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Abstract: In developmental psychopathology, differentiating between the coexistence and the clinical entity of two problem areas is of utmost importance. So far, logistic regression analysis has already provided helpful answers, as shown in studies on comorbidity of tic disorders. While the concept of *bridging symptoms* may be investigated adequately by both logistic regression and the network approach, the former (latent variable) seems to be of advantage with regard to the problems of multiple comorbidities and development.

In this commentary, we use *comorbidity* to refer to the co-occurrence of two diagnoses at the same time for a single patient, independently of etiological and/or pathway considerations (see Banaschewski et al. 2007). In children's mental disorders, comorbidity plays an even greater role than in adults: about 80% of children develop at least one comorbid condition compared with 45% in adults (Cramer et al., target article; Freeeman et al. 2007; Gillberg et al. 2004). However, parents and physicians prefer to restrict the necessary multimodal treatment regime to only one disorder (i.e., a clinical entity). Therefore, in children it is highly important to determine whether or not the coexistence of two mental disorders represents a separate clinical entity (i.e., true comorbidity) with the possibility of a specific treatment (Banaschewski et al. 2007; Cramer et al., target article). To approach this issue, the concept of "overlapping" or "bridging" psychopathology between two problem areas comes into play. For example, the coexistence of tic disorders (TDs) and attention-deficit hyperactivity disorder (ADHD) presents an important practical problem for diagnosis and treatment in child psychiatry (Rothenberger et al. 2007). First, some direct overlap exists between symptoms of hyperactivity, impulsivity, and inattention, and, second, there is some indirect overlap because TD and ADHD are both associated with the same disorders (e.g., Asperger Syndrome, anxiety, depression, obsessive-compulsive disorder [OCD]).

Thus, it is of practical importance to disentangle which symptom dimensions are actually overlapping and which ones are distinct between TD and ADHD. And does an overlap of symptoms indicate that TD + ADHD represents a separate clinical entity?

In order to answer these questions, we think that a 2×2 factorial design, analyzing "pure" groups and their combination (i.e., without further comorbid conditions like anxiety or depression) is more appropriate and practically relevant than a network approach, because the factorial design creates a clearer and clinically adaptable picture for guiding treatment. So far, several studies using this approach have shown that TD + ADHD is not a clinical entity and that its comorbidity needs to be explained within the framework of an additive model (Rothenberger et al. 2007). Using the Child Behavior Checklist as a psychopathological screener, both TD and ADHD showed similar scores for the anxiety/depression, schizoid/obsessive, and social withdrawal scales, whereas only ADHD reached statistical main effects for aggression, delinquent behavior, and attention and social problems (Roessner et al. 2007b). These results also clarify that internalizing problems should not be neglected in TD + ADHD, nor in primarily externalizing disorders like ADHD (see also, Sobanski et al., in press). Further, the results underline that boundaries between both mental disorders are partly fuzzy while also displaying distinct features, a conclusion which, methodologically, might also be reached by using the network approach. Applying both approaches to the same data set could be helpful in order to detect their scientific strengths and weaknesses. At least, both statistical approaches stress that *bridging symptoms*, the correlation of latent variables and interacting networks, must be carefully controlled for in clinical trials since they are possible confounders of mental disorders.

Further, relations between symptoms may vary according to a patient's age, his/her stage of development, gender, and changes in other symptoms. To provide a long-term dynamic view of comorbid psychopathology, it would be of great interest to evaluate the advantages of a network approach in developmental psychopathology research when investigating the stability and change of certain disorders, symptom clusters, and/or behavioral dimensions along the life-span. For example, there is a high stability of ADHD symptoms from ages 9–14 (Larsson et al. 2004). Subsequent follow-up at ages 16–17 has indicated that hyperactivity-impulsivity decreases, while inattention remains the same (Larsson et al. 2006). Changes in ADHD subtypes and comorbidity have also been reported (Lahey et al. 2005; Steinhausen et al. 2010). So far, logistic regression analyses have mainly been used and have already provided some practically useful answers in regard to the development of comorbidity (Roessner et al. 2007a; Wanderer et al., submitted).

In their introduction (target article, sect. 1), Cramer et al. ask whether there is a general order in which people develop a particular disorder first and then another next. We would add here that there might be a third disorder, as can be seen in daily clinical practice in child psychiatry when faced with psychosocial impairment caused by comorbidity.

For example, TD has a childhood onset and follows a remitting course into adulthood. Comorbid ADHD commonly antecedes TD and remains after tic remission, whereas comorbid OCD starts later than tics and often remains longer than ADHD. Unfortunately, developmental psychopathology with more than one comorbidity has received minor attention to date, and it would be a challenge for a network approach to disentangle this complex issue. Using logistic regression, Roessner et al. (2007a) analyzed, in children and adolescents with TD, the impact of comorbid ADHD diagnosis on the frequency of additional (third) comorbidities during development. The main finding was that ADHD generally increased comorbidities in all age groups (especially the externalizing problems), with the exception of adolescent OCD and anxiety disorders. In addition, there was a higher annual rate of change in emotional problems compared to externalizing disorders. This indicates the importance of an increase in internalizing problems with age for comorbidity research in youngsters and underlines that multiple comorbidity is a relevant issue that needs to be dealt with.

It is hard to imagine how a network approach could solve this problem in a scientifically better and practically more useful way, since too many interactions over time may reduce clarity. On the other hand, these manifold interactions between symptoms, changing over time, reflect reality. Hence, a network approach can be successful in this matter only if a statistical way is found to reduce complexity without loosing validity.

In sum, the network approach should be evaluated in developmental psychopathology mainly for theoretical reasons while its practical value for a better understanding and treatment of young patients has yet to be proven. Such a research perspective should include not only the level of clinical symptoms, but also the area of neuropsychological and neurobiological parameters. This may allow us to define new endophenotypes, which might in turn help to further elucidate the comorbidity pathway from genes to behavior.

Comorbidity: Cognition and biology count!

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Abstract: We agree with Cramer et al. that pure cases of behavioral disorders with no symptom overlaps are rare. However, we argue that

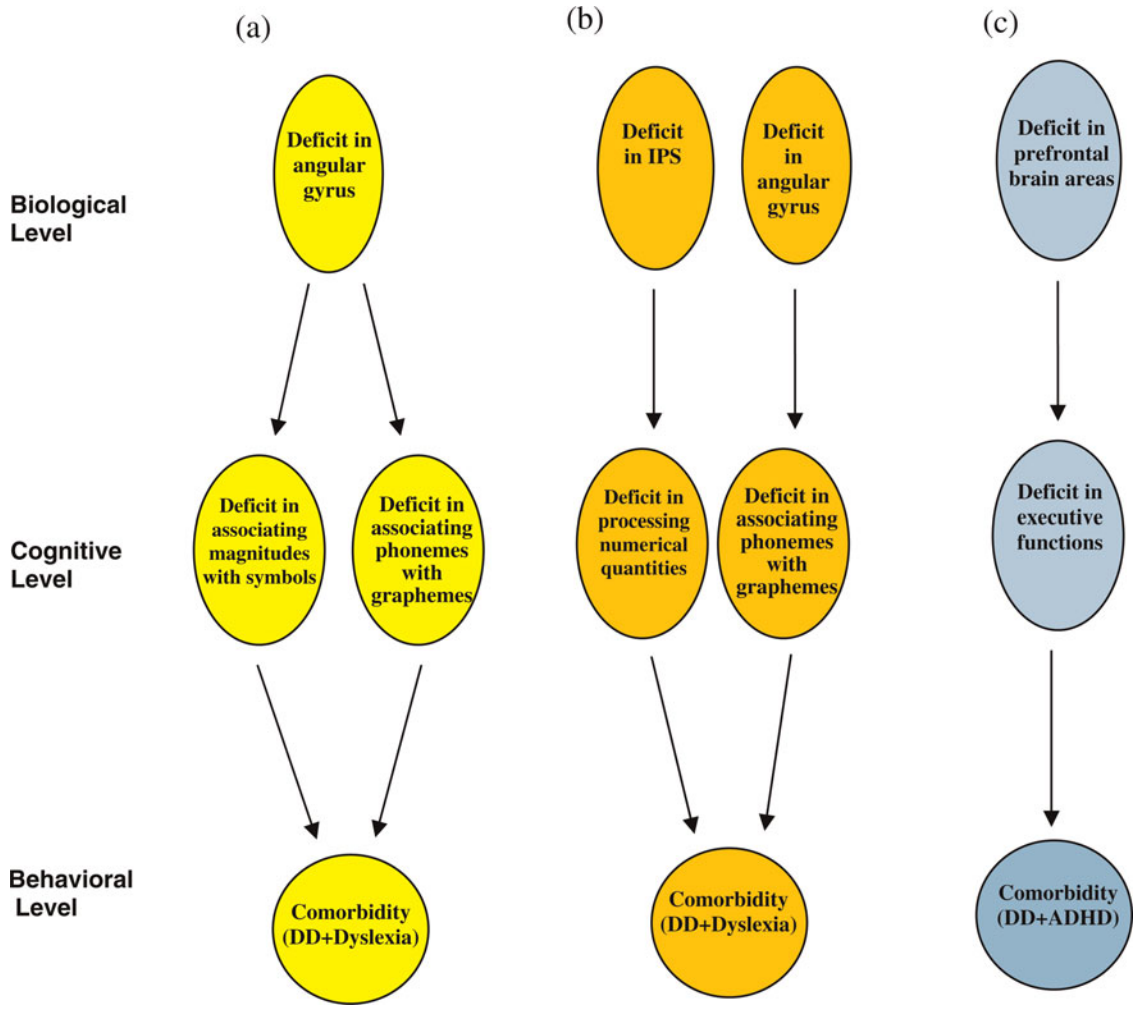

Figure 1 (Rubinsten and Henik). Three alternative frameworks for the origins of comorbidities. IPS, intraparietal sulcus. (a) A unique pathophysiology resulting in a network of behavioral symptoms. (b) Multiple brain dysfunctions resulting in a network of behavioral symptoms and (c) A unique pathophysiology resulting in a behavioral disorder that is a risk mechanism for another disorder.

disorders do exist and the network idea is limited and limiting. Networks of symptoms are observed mainly at behavioral levels. The core deficit is commonly at the cognitive or brain levels, and there the story is completely different.

We argue that latent variables, argued against by Cramer et al. in the target article, exist at the cognitive and biological levels. Interestingly, when we searched Cramer et al.'s article, the word *brain* was not mentioned even once, the words *gene* and *cognitive* were mentioned twice, and the word *cognition* was mentioned only once. If only the behavioral level is taken into account, the suggested network model may be correct. However, core features of mental disorders are best understood in terms of deficits at the cognitive and the biological levels (e.g., Frith 2001). Specifically: (1) Core ("common cause") deficits at the cognitive or brain level may show up as a network of symptoms similar to that suggested by Cramer et al., even when there is a single deficit. (2) A single deficit at the behavioral or cognitive level may produce, through development, a cascade of difficulties (Rutter & Sroufe 2000) that may end up as comorbidity (i.e., look like a network of symptoms at the behavioral level). (3) Revealing the core deficit will lead to a more exact diagnosis, which would encourage specific intervention programs.

We discuss developmental learning and behavioral disorders. A most remarkable finding is the specificity of these disorders: highly intelligent children who excel in many different ways, have a specific cognitive disability. This one specific cognitive gap may hamper, through development, many types of behaviors, including those that are relevant to other abilities, resulting in comorbidity or in "a network of symptoms." Here we give examples of mathematics disorder, reading disorder, and attention-deficit hyperactivity disorder (ADHD) to further strengthen our argument.

Mathematics and reading disorders. Five to seven percent of children experience difficulties in learning mathematics and/or reading though they are not of low intelligence and do not suffer from educational deprivation (von Aster & Shalev 2007; Wilson & Dehaene 2007). Current research suggests that these learning disabilities, known as *developmental dyscalculia* (DD) and *dyslexia* (for reading), are due to underlying brain dysfunctions (see, e.g., Cohen Kadosh et al. 2007; Kucian et al. 2006; Shaywitz & Shaywitz 2008). Similar to depression and generalized anxiety, DD and dyslexia, recognized psychiatric disorders (under different terms such as *mathematics disorders* or *reading disorders*; American Psychiatric Association 1994) are appropriate to test Cramer et al.'s main arguments.

It has been suggested that DD reflects deficiency mainly (but not only) in brain regions of the parietal cortex, along the intraparietal sulcus (IPS). IPS deficiencies can be found at the structural level (Isaacs et al. 2001; Rotzer et al. 2008) and the functional level (e.g., DD in adults [Cohen Kadosh et al. 2007;

Holloway & Ansari, in press]; DD in children [Kaufmann et al., in press; Kucian et al. 2006; Mussolin et al., 2010; Price et al. 2007]). The IPS is considered to be involved with an abstract, amodal representation of numbers (Cantlon et al. 2009; Dehaene 2009). The IPS is also activated by numbers presented in symbolic notations such as Arabic numerals and spoken number words (Eger et al. 2003). Despite indecisiveness in existent developmental imaging studies (e.g., Kucian et al. 2006; Price et al. 2007), deficiency in the IPS functioning is the best-validated core deficit or, in Cramer et al.'s terminology, the common cause of DD (Wilson & Dehaene 2007). This in itself does not fit the description of multiple behavioral symptoms organized in a connected network with no latent variable.

Importantly, the unique pathophysiology of DD is frequently accompanied by heterogeneous behavioral deficits. Moreover, this is the case in many other developmental disorders (Karmiloff-Smith 2006) – multiple problems are the rule, and pure disorders apply only to a minority of cases. Twenty to sixty percent of children with DD have associated learning problems such as dyslexia (von Aster & Shalev 2007). What is the reason? We (Rubinsten & Henik 2009) have suggested two main alternative hypotheses for the origin of comorbidity of DD and dyslexia: (1) *A single brain injury may cause DD* and include a risk mechanism for dyslexia (see our Fig. 1, panel a). For example, a deficient ability to automatically associate written symbols with mental representations such as quantities or phonemes may lead to math and reading difficulties. In this case, a specific brain lesion produces a cognitive difficulty, and a network of symptoms may appear at the behavioral level but not necessarily at the cognitive or biological levels. (2) *DD + dyslexia could be due to several brain dysfunctions* – for example, one in the IPS (Price et al. 2007) resulting in DD, and the second in the left peri-sylvian brain areas (McCandliss & Noble 2003) resulting in dyslexia (see Fig. 1, panel b). Landerl et al. (2009) have suggested that dyslexia and dyscalculia have separable cognitive profiles (i.e., a phonological deficit in dyslexia and a deficient number module in DD) that simply appear together. This does not support Cramer et al.'s network theory.

Attention-deficit hyperactivity disorder (ADHD). One developmental disorder may be a risk mechanism for another; an example follows. ADHD is a neuropsychiatric disorder that is characterized by inattention, impulsivity, and motor restlessness (American Psychiatric Association 1994; Bush 2010). Individuals with ADHD manifest unexpected problems in mathematics that cause impairments in academic achievement and daily functioning, with estimates ranging from 10% to 60% (Mayes et al. 2000). Some attribute the significant mathematical delays in children with ADHD to attention-based impairments (Lindsay et al. 2001) or working memory (Rosselli et al. 2006). These general cognitive impairments (i.e., not specific to mathematics) are considered to be integral features of the ADHD syndrome and, hence, may cause mathematical difficulties in some of these children (i.e., DD + ADHD) (Barkley 1997; Castellanos et al. 2006) (see Fig. 1, panel c).

To summarize, DD, dyslexia, and ADHD are specific neurodevelopmental psychiatric disorders, but they are rooted at the biological and cognitive levels, and are only indicated by behavioral signs. Therefore, even if at present research regarding such biological and cognitive deficits is not always conclusive, it can better serve as a basis for testable predictions.

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Looking at comorbidity through the glasses of neuroscientific memory research: A brain-network perspective

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Abstract: As psychiatric illnesses have correlates in the brain, it is surprising that Cramer et al. make almost no reference to the brain's network character when proposing a network approach to comorbidity of psychiatric diseases. We illustrate how data from combined neuropsychological and functional and structural brain-imaging investigations could inform theoretical models about the role played by overlapping symptoms in the *etiology* of psychiatric comorbidity and the pathways from one disorder to another.

Comorbidity with substantial overlap of symptoms can be found in a number of disease conditions, apart from the generalized anxiety disorder (GAD) and major depressive disorder (MDD) analyzed by Cramer et al. in the target article – for example, between bipolar disorder, attention-deficit hyperactivity disorder (ADHD), and severe mood dysregulation. Furthermore, ADHD is often comorbid with bipolar disorder. "Severe mood dysregulation" is non–*DSM-IV-TR* terminology (*Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision*; American Psychiatric Association 2000) that describes a condition in children which comprises a constellation of symptoms of ADHD, oppositional defiant disorder, and MDD (Hudziak et al. 2007).

Deficits of face-emotion processing were reported in major depressive disorder, bipolar disorder, severe mood dysregulation, and ADHD. The investigation of face-emotion processing with functional magnetic resonance imaging (fMRI) provided evidence of distinct neural correlates among youth (children and adolescents) with bipolar disorder, ADHD, and severe mood dysregulation (Brotman et al. 2010). The neural (amygdala) activation during face-emotion processing in youths with severe mood dysregulation resembled the neural pattern reported in youths with MDD. This is of particular interest given longitudinal studies indicating that severe mood dysregulation in youths leads to subsequent depressive episodes (Brotman et al. 2010). These results therefore provide an example of how neuropsychological investigations combined with brain imaging may scientifically test the significance of overlapping symptoms for the etiology of comorbidity and may even aid in predicting the progression from one disease to another.

Memory research data could also inform a network conceptualization of comorbidity by offering a perspective that is grounded in evidence about brain organization and development and takes into account variables such as age, gender, and developmental phase. Though not listed under the *DSM-IV-TR* (APA 2000) diagnostic symptom criteria, impairments of episodic-autobiographical memory are frequently described in MDD (Beblo & Herrmann 2000; Williams & Scott 1988) or bipolar disorder. Furthermore, several psychiatric disorders (e.g., dissociative amnesia) and neuropsychiatric disorders (e.g., mild cognitive impairment [MCI], Alzheimer's dementia) characterized by alterations of episodic-autobiographical memory can be comorbid with MDD. Also, in stroke conditions, temporal lobe epilepsy, and multiple sclerosis, both

MDD and episodic-autobiographical memory deficits could be present.

From a neuroscience perspective, an analysis of the nature of the co-occurrence of memory and emotional disorders includes references not only to genetic polymorphisms, but also to brain mechanisms such as extent of insult (lesion penumbra), shared vasculature, axonal innervations (branching, bifurcation) or brain metabolism (neurotransmitters, enzymatic pathways), and a desynchronization or disconnection of otherwise integrated brain networks. The latter may underlie several psychiatric symptoms, including the co-occurrence of emotional processing and episodic-autobiographical memory impairments, as illustrated further on.

It is accepted that specialization and integration characterize the human brain and that cognition and emotion are integrated through structures with a high degree of connectivity (*hubs*; Pessoa 2008). Functional neuroimaging has provided evidence for abnormalities of functional connectivity between spatially distanced brain areas, underlying several psychiatric symptoms. Recently, the combination of functional and newer structural imaging techniques (diffusion tensor imaging) began to unearth (micro-)structural correlates for various functional connectivity dysfunctions, in particular white matter (long-range fiber tracts) abnormalities (Catani 2007; Paus et al. 2008). Evidence for white matter changes in several psychiatric disorders comes also from genetic and anatomo-pathological research. Postmortem studies of patients with MDD revealed glial cell loss (Rajkowska et al. 1999). Dysfunctions of oligodendrocytes or genes involved in myelination have been reported both in patients with MDD and in those with bipolar disorder (Lee & Fields 2009). Apart from genes, sex hormones are involved in a gender-differentiated modulation of white matter reorganization in adolescence (Paus et al. 2008). Environment and experience could also exert influences on white matter development, partly via epigenetic regulation of gene expression in myelinating cells (Casaccia-Bonnefil et al. 2008). In children with a history of early deprivation, an overgeneral memory effect (Valentino et al. 2009), as well as changes in fiber tracts (including the uncinate fascicle [UF]), have been described (Govindan et al. 2010).

The anatomy and function of UF suggest that it may be one pathway of co-occurrence of emotional and memory disorders. UF integrates memory with emotion and links portions of the frontal and temporal lobes. Its ventromedial part connects the amygdala and uncus with the gyrus rectus and the subcallosal area (Ebeling & von Cramon 1992) (Fig. 1). The UF partly intermingles with the anterior commissure and the inferior occipitofrontal fascicle. It matures later than other connections and may continue its development beyond 30 years (Lebel et al. 2008).

The ventral right UF is involved in the retrieval of episodic-autobiographical memories, in particular in ecphorizing affect-laden personal events. The UF also belongs to an emotional processing circuitry that connects the amygdala with the orbitofrontal cortex and the anterior cingulate cortex.

The role played by the right UF in the retrieval of episodic-autobiographical memories has been underlined by several studies of memory performance in patients with neurological insults as well as in normal people (Fink et al. 1996; Levine et al. 1998). Furthermore, the relevance of the UF for declarative memory in general has received support from many researchers who described a connection between UF structural alteration and memory performance in temporal lobe epilepsy (Diehl et al. 2008), multiple sclerosis (Sepulcre et al. 2008), and Alzheimer's disease (Yasmin et al. 2008). In their study of amnestic MCI, Fujie et al. (2008) reported both memory and emotional recognition impairment together with abnormalities of the UF. Consistent with the proposed role of UF in emotional processing, recent evidence suggests that disruptions in functional fronto-limbic connectivity described in MDD, bipolar disorder, and anxiety disorders may have UF microstructural changes as substrates (Phan et al. 2009; Taylor et al. 2007; Wang et al. 2009).

Altered connectivity between brain areas involved in memory and emotional processing may also underlie the commonly observed comorbidity between dissociative amnesia and MDD (Maldonado & Spiegel 2008). Evidence for functional disconnections between these areas in dissociative amnesia was provided in a study by Brand et al. (2009). In this study functional brain imaging performed in a resting state in 14 patients with dissociative amnesia evinced malfunctions of the right temporofrontal regions with a common significant hypometabolic zone in the right inferolateral prefrontal cortex. As Tramoni et al. (2009) have found, these malfunctions may reflect subtle structural right-hemispheric prefrontal white matter abnormalities.

Regarding the directionality of the links between emotional disorders and episodic-autobiographical memory impairments, it seems perhaps intuitive that one pathway flows from emotional disorders to episodic-autobiographical memory impairments via a defect in emotional processing. Memory research, however, provides grounds for an additional, less intuitive pathway, which may run from episodic-autobiographical memory impairments to the emotional disorders. In this regard, recent data emphasize that episodic-autobiographical memory has a significant proscopic function. Neuroimaging studies have revealed that similar networks, which serve episodic-autobiographical memory, are engaged in self-projection and construction of future events (Schacter & Addis 2009). A main characteristic of patients with MDD is the inability to imagine an optimistic future (Sharot et al. 2007), which may lead them to attempt suicide. It is plausible that this inability may reflect a disruption of the balance between the neural networks that subserve the encoding and retrieval of positive versus negative episodic-autobiographical memories (Markowitsch et al. 2003).

In conclusion, we agree that shortcomings characterize current psychometric conceptualizations of psychiatric diseases, warranting a more in-depth psychometric thinking and the advent of new conceptualizations. We suggest, however, that the development of a theoretical network approach to psychiatric diseases should rely on an iterative relationship between psychometric analysis and neuroscience, which would enable refinements of the network approach.

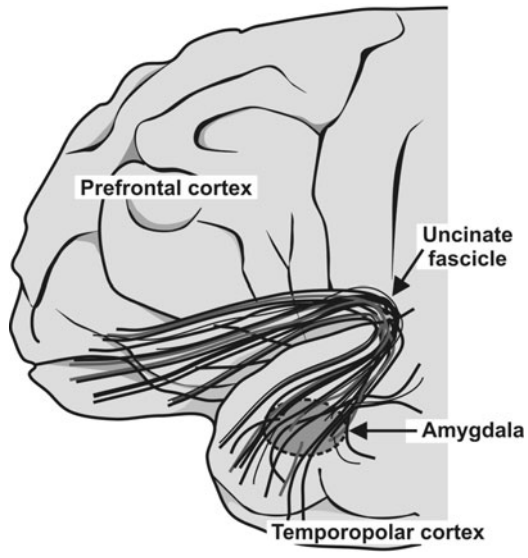

Figure 1 (Staniloiu and Markowitsch). Lateral view of the frontal cortex showing the course of the fasciculus uncinatus.

The importance of modeling comorbidity using an intra-individual, time-series approach

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Abstract: We suggest that the network approach to comorbidity (Cramer et al.) is best examined by using longitudinal, multi-measurement, intra-individual data. Employment of time-series analysis to the examination of the generalized anxiety disorder and major depressive disorder comorbidity enables a detailed appreciation of fluctuations and causal trajectories in terms of both symptoms and cognitive vulnerability.

We are fascinated with the compelling challenge posed by Cramer et al. to the latent variable approach, and with their alternative, network approach to the understanding of psychiatric comorbidity. Whereas the determination of the empirical status of both approaches – latent and network – awaits future research, herein we argue that such research would greatly benefit from an intensive, intra-individual, longitudinal prospective study design, preferably using time-series analysis (TSA).

The preponderance of cross-sectional data pertaining to the anxiety and depression comorbidity often yields perplexing results. Most cross-sectional studies investigating comorbidity are in essence based on the assessment of prevalence, aimed at examining the likelihood of a secondary syndrome in the presence of a primary one. Studies applying such an approach generally tend to conclude that anxiety leads to depression (Breslau et al. 1995; Hettema et al. 2003; Kessler et al. 1996; Lewinsohn et al. 1997). As cited by Cramer et al., longitudinal, inter-individual studies focusing on point prevalence, suggest differently. Namely, these studies show that both disorders are equally likely to be the first in a comorbidity sequence (Moffitt et al. 2007). Moreover, longitudinal studies focusing on subthreshold symptomatology indicate that mixed presentation of anxiety and depression tends to culminate in either full recovery, or in pure presentation (Barkow et al. 2004).

While employing inter-individual, longitudinal research on comorbidity advances the field, herein we argue that the logic behind such studies should be taken further to examine intra-individual unfolding of symptomatology. In an ongoing project examining intra-individual trajectories, and associations, involving anxiety and depression, we find, first and foremost, intense fluctuations in symptoms, cognitions, and affective variants of both disorders. These frequent fluctuations across a 2- to 6-month period were unique to participants reporting elevated levels of *both* anxiety and depression. Such a pattern is sharply contrasted with the relatively stable manifestation of anxiety and depression in participants exhibiting, to begin with, elevated levels of either, but not both, anxiety and depression.

To illustrate, in Figure 1 we present the variability of fear, as representing the affective component of anxiety, in four participants initially assessed using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). Participants were also assessed as to their affect by using the PANAS-X (Positive Affect Negative Affect Schedule, expanded version; Watson & Clark 1994), for a period of 2 months, three times daily. Two of the four participants had elevated scores on both the BDI and BAI, and the remaining two had elevated scores on either. As shown in Figure 1 (top), participants with a mixed presentation exhibited marked fear fluctuations.

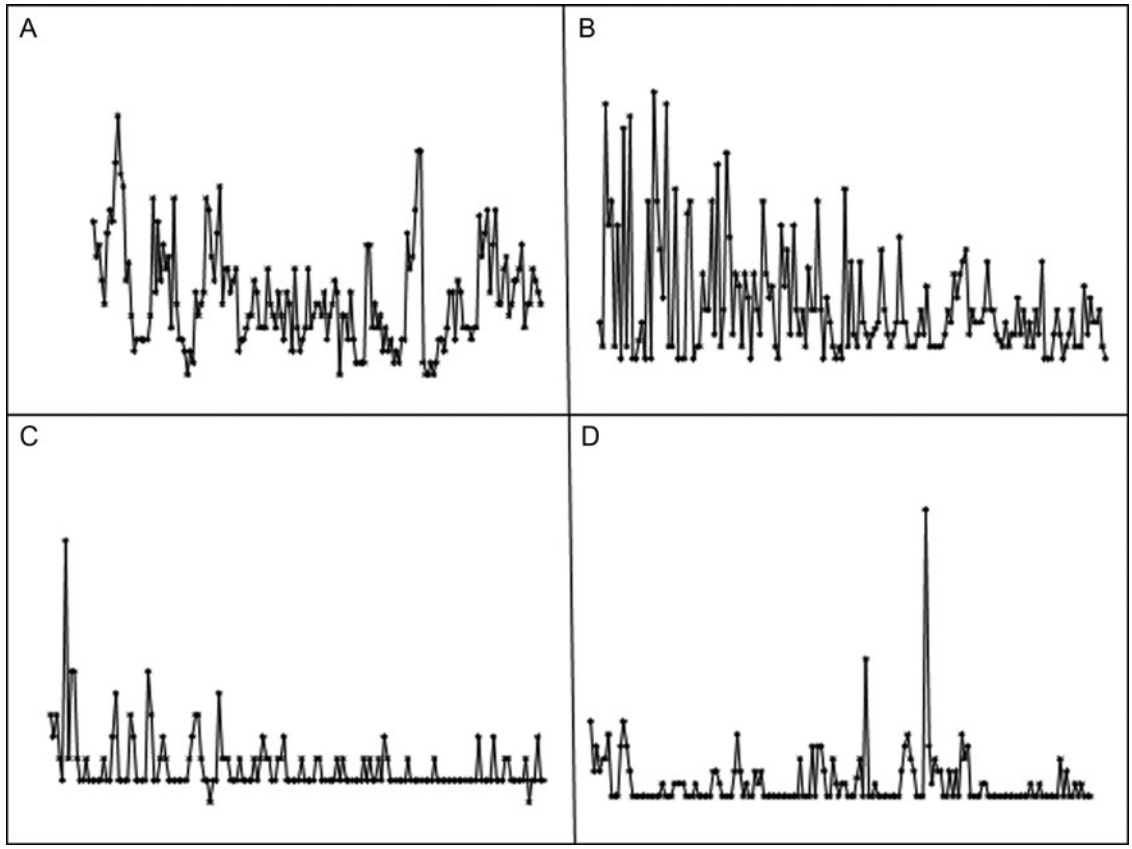

Figure 1 (Tzur-Bitan et al.). Plot of fear (PANAS-X; Watson & Clark 1994) across study assessment period. **A and B:** Variability in mixed anxiety and depression participants. **C:** Variability in anxiety participant. **D:** Variability in the depression participant.

Aimed originally for forecasting and control of economical and political trends, TSA involves describing and predicting the pattern of behavior of a variable based on its own past values, while considering the effects of slowly adjusted, gradual accumulation (namely, auto-regressive processes) versus local influences (moving-average processes). The most common and widely used technique for analyzing and forecasting time series is based on the Box and Jenkins (1976) methodology, which includes a three-step strategy for selecting the best forecasting model from a general class of regression-based models. Having selected a model, it then becomes possible to estimate parameters, check the goodness of fit to the data, and then use the fitted model to enhance understanding of the dynamic laws governing the investigated phenomenon. Box and Jenkins also offer a strategy for assessing causality by using transfer-noise function modeling, aimed at assessing the trajectory from an input series (such as an anxiety symptom) into a dynamic system and on to the output series (such as a depression symptom). Implementation of this approach enables the evaluation of the duration, direction, and intensity of influence of one construct on the other.

In another project, we examined three participants suffering from generalized anxiety Disorder (GAD) and major depressive disorder (MDD) comorbidity. These participants were followed up daily for an extensive period of 6 months, and TSA was utilized to determine fluctuations and trajectories. We found cognitive vulnerability to emerge as a key component shaping the causal network between symptoms of anxiety and depression. Specifically, in two of the three participants, the *looming maladaptive cognitive style* (LMCS; Riskind et al. 2000), pertaining to the tendency to generate mental scenarios of potentially threatening situations as rapidly rising in risk, was causally related to subsequent increase in depressive symptoms. As well, in two of the three, LMCS was causally related to a subsequent increase in hopelessness, itself a cognitive vulnerability dimension to depression. In none of the participants did symptoms of depression, or depressive vulnerabilities, cause subsequent increases in anxiety or its vulnerabilities. These findings are particularly intriguing because they suggest that cognitive vulnerability to anxiety might cause both depression and its specific cognitive vulnerability, but not vice versa.

Put in the context of Cramer et al.'s argument, our findings suggest that anxiety and depression are multidimensional, and that specific dimensions of anxiety (but not depression) are causally related to specific dimensions of depression. On the face of it, this is consistent with the network approach, and we hope that the use of TSA will shed further light on distinct causal configurations involving anxiety and depression.

Consequences of a network view for genetic association studies

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Abstract: Cramer et al's proposal to view mental disorders as the outcome of network dynamics among symptoms obviates the need to invoke latent traits to explain co-occurrence of symptoms and syndromes. This commentary considers the consequences of such a network view for genetic association studies.

Genetic association studies (henceforth GAS, used in the plural) aim to identify genes or genetic variants (GVs) that are systematically associated with variation on the behavioural level (Balding 2006; Hirschhorn & Daly 2005). In its exploratory form, GAS test the associations between 300.000-500.000 GVs typed across the entire genome and a phenotype of interest, which can be continuous or dichotomous, such as affection-status. For instance, consider a GV with two alleles: A and B. If allele A is more frequently observed in cases than in controls, then this allele A may be associated with an increased risk for the disease under study. Where successful, GAS are a first step towards revealing functional relations between the genome and behaviour. GAS have successfully localized GVs for medical conditions such as Crohn's disease (Zhang et al. 2009) and type-I diabetes (Barrett et al. 2009), but, despite high family-based heritability estimates, have been less successful for psychiatric traits. Disappointing results have been attributed to statistical problems (e.g., low power), genetic complexity (e.g., gene-gene interaction), and genetic heterogeneity (e.g., the genetic etiology of disease may vary across families). Incorrect characterisation of the phenotypic model, however, may also render GAS inefficient.

In the search for GVs associated with psychiatric disorders, symptoms are usually considered manifestations of an underlying latent trait, which causes the variance in the symptoms, and the observed relations between the symptoms. The ultimate aim of GAS is to identify the GVs that cause individual differences in the latent trait, as under this model the relations between GVs, on the one hand, and individual symptoms, on the other, are mediated by the latent trait. A common operationalization of a latent trait in GAS is the sum score calculated across all items or symptoms of a diagnostic test. The sum score can subsequently be subjected to dichotomization following diagnostic cut-off criteria. This score then features as the dependent variable in GAS, and GVs are used to predict the (dichotomized) sum score. Although the (dichotomized) sum score may be a crude approximation of the latent trait, the operationalization is consistent with the latent trait model.

In the network model proposed by Cramer et al., however, the observed relations between symptoms are not attributable to a common latent cause but result from the direct causal relations among the symptoms themselves. In this model, all symptoms could in principle have a unique genetic etiology, so the sum score operationalization could potentially be counterproductive in the search for GVs. One may ask, however, whether the high twin-based and family-based heritability estimates (h^2) for psychiatric disorders are consistent with Cramer et al.'s network view.

Under the network model, considerable h^2 estimates remain feasible for two reasons. First, calculations of h^2 are based on *within*-family comparisons. Researchers test, for example, whether monozygotic twins, who share 100% of their genetic material, are phenotypically more alike than dizygotic twins, who share on average 50% of their genetic material (Falconer 1989). If variance in symptoms is genetic in origin, then the genetic basis of the disorder is likely to be shared by members of the same family. Even if all symptoms have a different genetic etiology, and this etiology differs across families (i.e., genetic heterogeneity), family-based estimations of h^2 can be considerable because they are based on comparisons within families. Second, the direct causal interrelations between symptoms, such as described in the network model, will over time induce genetic correlations between symptoms that are initially genetically unrelated, that is, do not *functionally* share any genetic basis (as shown by van der Maas et al. [2006] in the context of intelligence). That is, with the passing of time, a common genetic factor may evolve from the phenotypic interactions between genetically unrelated symptoms, and the h^2 of the sum score may increase.

The fact that the h^2 of a sum score calculated across genetically unrelated symptoms can be substantial has important implications for GAS. Specifically, the high h^2 of sum scores does

not mean that this operationalization is useful in the search for the actual GVs of interest. The distinction between the network model and the latent trait model is thus essential in GAS: If the network model is the true model, then the common way geneticists operationalize their phenotypic information may be counterproductive. Under the network model, GAS on the individual symptoms, or even on the relations between the symptoms, as Cramer et al. suggest, make more sense. Of course, such an approach comes with its own challenges, such as the exacerbation of the problem of multiple testing (e.g., 10 symptoms may produce 1 sum score, but 10 symptom-level ones, and 45 relational tests).

At present, the network perspective of major depressive disorder (MDD) and generalized anxiety disorder (GAD) is quite speculative. A recent study by Lux and Kendler (in press), however, lends some credence to the network view of MDD. These authors showed that nine criteria for MDD (e.g., depressed mood, fatigue) displayed markedly different relations to factors such as risk for future episodes, risk of depression in the co-twin, and patterns of comorbidity. These results suggest considerable heterogeneity within the MDD syndrome, and are inconsistent with the idea that, within disorders, all symptoms are interchangeable indicators of a single causal latent trait. Although these results do not prove the network model, Lux and Kendler's findings are hard to reconcile with the latent trait model.

While GAS may benefit from a network approach to phenotypes, genetic studies may help to validate the network approach. Network models and latent trait models may yield quite similar phenotypic covariance structures (van der Maas et al. 2006). Behaviour genetics provides several research designs that are informative about causality, such as direction of causation models, the co-twin control design, the children-of-twins design, and Mendelian randomisation. In additional, possible genetic influence on the interrelationship among symptoms can be addressed using moderated genetic covariance structure modeling (Purcell 2002).

Like the latent trait model, the network perspective is a theoretical model, which still requires validation. If true, however, it constitutes an interesting alternative viewpoint and could have far-reaching consequences for GAS.

Networks as complex dynamic systems: Applications to clinical and developmental psychology and psychopathology

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Abstract: Cramer et al.'s article is an example of the fruitful application of complex dynamic systems theory. We extend their approach with examples from our own work on development and developmental psychopathology and address three issues: (1) the level of aggregation of the network, (2) the required research methodology, and (3) the clinical and educational application of dynamic network thinking.

Cramer et al.'s target article shows a fruitful application of a dynamic network perspective – or complex dynamic systems (CDS) perspective – to clinical psychology, in particular the comorbidity of depression and anxiety. This commentary addresses three issues that can place the article in a broader framework of CDS-oriented theory and research in developmental psychology and psychopathology.

A complex dynamic system (CDS) is as a collection of interconnected components – the network – which change one another's properties through the interconnections and out of which emerge collective properties, such as patterns or correlations (Van Geert 2009). These patterns correspond with macroscopic phenomena (e.g., depression, attention-deficit hyperactivity disorder [ADHD], developmental levels). We believe that CDS theory provides a coherent conceptual and methodological tool-kit for understanding virtually all interesting phenomena of emergence in the behavioral sciences.

Cramer et al.'s network of causal influences is based on actual phenomenal appearances – symptoms – and not on underlying entities, such as depression, that correspond with latent variables. Assigning the causality to the actual phenomena instead of underlying entities is typical of the dynamic systems approach (e.g., Thelen & Smith 1994; van der Maas et al. 2006). Our own work provides examples of a CDS approach to long-term cognitive and language development, based on the interaction of components in a network of variables (e.g., Bassano & van Geert 2007; Fischer & Bidell 2006; Steenbeek & Van Geert 2007; 2008; Van Geert 1991; 1994; 1998; Van Geert & Steenbeek 2005). In an ongoing project, we have formulated a dynamic work model for explaining science and technology talents in young children (see Van Geert & Steenbeek, submitted).

The first question we address concerns the chosen level of aggregation for defining the dynamic network. Cramer et al.'s network is a structure of intra-personal symptoms, leading to comorbidity of depression and generalized anxiety. Our own approach to problematic learning trajectories in children with ADHD and PDD-NOS (pervasive developmental disorder, not otherwise specified) is based on the concept of a *distributed network*; that is, variables distributed over a child, an educator, and a material context. We view disorders such as ADHD as attractor states, consisting of fuzzy and variable ensembles of symptoms, actions, emotions, contexts, actions of the educators, and so on. These components affect one another in that they call forth one another's appearance in particular contexts. The interactions between components result in the consolidation of a particular pattern – for instance, one that educators or psychologists identify as the underlying condition ADHD, which they see as the "deep" causal mechanism of the symptoms. Our view is highly comparable to Cramer et al.'s view on clinical symptoms as *attractor states*; that is, self-sustaining patterns of mutually attracting symptoms. Our main goal is to use the short-term dynamics of relationships between variables (e.g., what happens during a concrete child-educator interaction) to explain the long-term trajectories through the state space of variables, which leads to the kind of self-sustaining states diagnosed as ADHD and the like.

Our distributed network shows a nested structure, with the child, the educator, and the educational materials as the main nodes, each comprising lower-level networks of variables specific to each of the main nodes (for an example of such a nested dynamic system, see our work on dyadic play interaction in children; Steenbeek & Van Geert 2007; 2008). The distributed network can be described from the perspective of each of its main nodes. For instance, from the perspective of the child, the educator and the educational materials constitute what is commonly called the context of the child's actions. Such contexts are not to be treated as independent variables. They are dynamically co-determined as part of the network (see Steenbeek & Van Geert 2007; 2008). They can change abruptly (e.g., if the child changes classes or activities), which may lead to relatively abrupt changes in the temporal attractor state (e.g., the actual expression of the child's ADHD), thus helping to explain the characteristic intrapersonal variability of a particular child's ADHD condition (see, e.g., Van Geert & van Dijk 2002).

Cramer et al. emphasize the variations in connection strength between nodes, defining the nodes' *degree of centrality*, that is, importance in a particular network. Superficially similar constellations of symptoms under the umbrella term of ADHD, for

instance, can be based on networks of different composition; that is, with different variables being more or less dynamically central, dependent on the particular individual in a particular context.

This brings us to our second issue, which is that of empirical design and methodology. In line with Cramer et al., we argue that networks emerge in the form of individual trajectories, and should therefore be studied with a time-serial case methodology. We study dynamic networks by directly observing the child's problematic learning in the class. We combine the observation of the short-term dynamics in a particular child – what happens during a single math lesson – with an account of the child's long-term dynamics, that is, changes in the patterning of the relationship between the components over the course of months or years (Steenbeek & Van Geert, submitted). This approach is *ideographic*, that is, it requires individual case studies. *Generalization* pertains primarily to the relationship between individual cases and the underlying CDS theory and only secondarily to sample generalization (see also Cramer et al's reference to Molenaar 2004; cf. Van Geert, in press).

Our third issue concerns the clinical or educational application of complex dynamic network models. We believe that a practitioner's qualitative insight into a dynamic network explanation of clinical phenomena – for example, child psychopathologies – will lead to a different practice than one based on a theory of "deep" causes (e.g., the latent variable ADHD as a causal explanation of observable ADHD symptoms). An approach based on an understanding of the fuzzy and dynamic boundaries between disorder and normality may help practitioners to view their actions as part of an interconnected dynamic network, and may help them to redefine the kind of control problem they have to solve in order to help children overcome their clinical and behavioral problems.

The missing developmental dimension in the network perspective

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Abstract: We welcome network theory as a tool for modelling the multi-directional interactions that characterise disease. However, we feel that Cramer et al. have neglected one important aspect: how diseases change over developmental time. We discuss principles such as *fan in*, *fan out*, *bottlenecks*, and *common pathways*, and argue that modelling these developmental aspects can be vital, particularly in deriving properly targeted treatments.

We welcome the central distinction offered in the target article between a latent-variable (i.e., disorder based) and a network theoretical (i.e., symptom based) approach to epidemiology. We have also argued (e.g., Karmiloff-Smith 1992; 1997; 1998; 2007; 2009; Thomas & Karmiloff-Smith 2002) in favour of approaches to typical and atypical development that emphasise multi-directional interactions between genes, brain, cognition, behaviour, and environment. Network theory offers precisely such an approach. We also agree with the authors that it is valuable as a way of offering potentially "truer" descriptions according to which diseases are defined as patterns of covariance of symptoms.

In their conclusion, Cramer et al. briefly discuss the potential usefulness of dynamic approaches to network modelling as a way of describing features such as bistable depressive states (Van der Maas et al. 2006; see also Rolls et al. 2008) It is disappointing, however, that the authors do not discuss another equally vital aspect: namely, the actual growth of networks, how patterns of symptoms evolve over developmental time.

In attempting to understand diseases, it is not sufficient merely to examine what their symptoms look like in an adult state. Particularly for deriving treatments and interventions, it is vitally important to track the progress of diseases throughout ontogeny to maturity. In doing so, a number of vital features can become apparent:

First, symptoms can *fan out* over time: that is, a small, basic-level deficit can, during development, lead to impairments in a variety of domains. So, for instance, an impairment in a *hub* cognitive domain such as executive attention (Cornish et al. 2007; Scerif et al. 2005) can, if present during particular sensitive periods, impede development across a variety domains such as number, language, and other aspects of social development. Thus, one symptom can lead over developmental time to a range of other symptoms, a causal relationship that may be revealed only if the developmental perspective is considered.

Second, particular symptoms can *fan in*: that is, conditions can converge on a *common pathway*. One example here may be autism, where various authors (e.g., Anderson et al. 2008; Chauhan et al. 2010; Herbert 2005) have hypothesised that a variety of different genetic vulnerabilities (i.e., discrete etiologies) may all converge on causing over-zealous neuroinflammatory responses early in neural development. These inflammatory and oxidative stressors early in development might, in turn, fan out (i.e., disrupt subsequent development in a range of ways), leading to many of the behavioural features that we recognise as the autistic spectrum behavioural phenotype. Again, it is only by adopting a developmental approach that such common pathways (or *bottlenecks*) may become evident; and yet they may offer potentially vital targets when developing treatment.

Similar principles of fan in and fan out can also go some way to explaining comorbidity, and to patterns of covariance of symptoms between different conditions. Thus, for example, any condition associated with impaired executive attention early in development (including, in various forms, Williams syndrome, Down syndrome, fragile X syndrome, and autism) may lead to partially similar patterns of impaired performance, which may then diverge again later in development (Cornish et al. 2007).

Another example of how developmental cascades operate can be gleaned from the neurodevelopmental disorder, Williams syndrome (WS; Donnai & Karmiloff-Smith 2000). Infants and toddlers with WS are very impaired early on in planning saccadic eye movements (Brown et al. 2003). This affects their subsequent ability to follow pointing (Laing et al. 2002), which in turn is detrimental to their ability to use parental referential pointing to learn vocabulary. So, although their language becomes proficient (not "intact"; Karmiloff-Smith 1998 much later in development, initially language in toddlers with WS is extremely delayed and follows a deviant developmental trajectory (Annaz et al. 2008; Paterson et al. 1999). Thus, an early problem within the *visual* system, together with other contributing factors (Masataka 2001; Nazzi et al. 2003), dynamically influences the way in which *auditory* stimuli are acquired and, because of the need for a critical vocabulary mass before syntax can take off, it is a visual deficit that is at the root of serious delays in grammatical development. Moreover, the failure to plan efficient saccadic eye movements doesn't only affect the learning of language. Individuals with WS also turn out to be predominantly featural processors, obvious from both brain and behavioural studies (Karmiloff-Smith et al. 2004; Grice et al. 2001; 2003; Mills et al. 2000). A possible explanation for this is that, in the typical case, rapid configural processing emerges from rapid scanning of stimuli via rapid eye movement planning whereas, in the atypical WS case, remaining fixated on a stimulus (e.g., a face) leads to a focus on featural detail. Individuals with autism are also featural analysers, yet the developmental pathway that leads to this end product may be different from the pathway

that leads to featural processing in WS. Again, only a developmental approach, particularly using cross-syndrome comparisons, can reveal the dynamics of the differing routes from infancy to the mature state in adulthood. And associations across syndromes might be more informative than the search for dissociations (Karmiloff-Smith 2009; Karmiloff-Smith et al. 2003).

There is an increasing awareness that it is important to study not simply a "snapshot" of symptoms in the mature state, but also the process by which they were reached. In terms of network theory, this poses considerable but not (we think) insuperable demands on the modelling techniques that are used. Useful cross-discipline approaches may come from work on the development and evolution of social networking (e.g., Backstrom et al. 2006; Kumar et al. 2006), where plentiful data are available for all stages of network development, throughout ontogeny. Data from the very early phases of diseases (when the critical building blocks are laid, but before a clinical diagnosis can be made, as is often the case in autism, dyslexia, and dyscalculia) are often harder to come by, which is why conceptual insights from other areas of network science may be so useful.

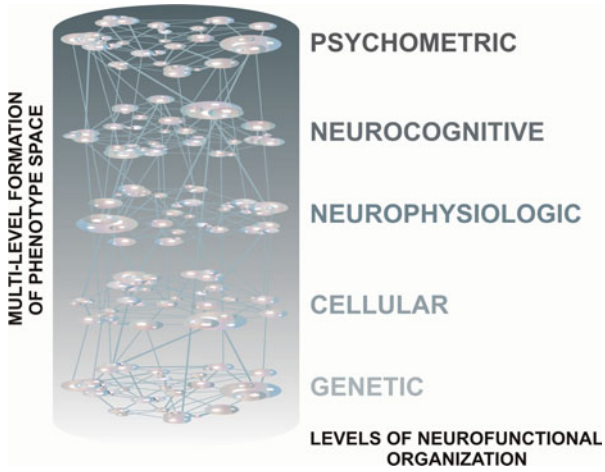

Figure 1 (Yordanova et al.). A theoretical extension of Cramer et al.'s Figure 4 demonstrating the multilevel formation of phenotype space.

Comorbidity in the context of neural network properties

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Abstract: Cramer et al.'s network approach reconceptualizes mental comorbidity on the basis of symptom space originating from psychometric signatures. We argue that the advantages of this approach need to be regarded in the context of the multi-level functional organization of the neural substrate, ranging from neurogenetic to psychometric. Neuroelectric oscillations are proposed as a level-integrating principle.

A network perspective on psychopathologic comorbidity is proposed by Cramer et al. as an alternative to the latent variable theory. The authors state that the network approach offers a radically different conceptualization wherein comorbidity is hypothesized to arise from direct relations of symptoms of multiple disorders, rather than from the relationship between sources of these disorders. Here, we argue that the advantages of the proposed perspective need to be viewed not only in the context of psychometry-based latent variable theory, but also in the context of existing neurophysiologic models for comorbidity.

Based on a series of neurophysiologic studies of comorbid child psychiatric disorders (attention-deficit hyperactivity disorder [ADHD] and multiple tic disorder [TD]; Yordanova et al. 1996; 1997; 2006), we have proposed a multi-level scheme of comorbidity. According to this model (Yordanova et al. 2006), the TD + ADHD comorbidity can be specified at several different levels, ranging from neurogenetic and neurobiological to neurophysiologic and psychometric. The following argumentation is used.

Transcranial magnetic stimulation (TMS) findings have substantiated the additive model for TD + ADHD (Moll et al. 2001), according to which the comorbid condition is an expression of the combination of independent nosologies. Since TMS measures reflect the background state of motor system excitability, basic subcortical-cortical (striato-thalamo-cortical) loops controlling the output from the cortical motor system (e.g., Leckman 2002) appear to be differentially impaired in TD and ADHD, and these impairments co-contribute separately in TD + ADHD comorbidity. Similarly, other basic neurophysiologic processes, such as sleep and its regulation, have been found to be altered differentially in TD and in ADHD, and, also consistent with the additive model, a combination of independent TD- and ADHD-related sleep disturbances was present in TD + ADHD (Kirov et al. 2007a; 2007b). Likewise, the spontaneous theta EEG activity reflecting background neuroelectric brain states has been found to differentiate the TD and ADHD conditions, but not to distinguish the comorbid group, which further supports the additive model.

However, event-related potential studies demonstrate that when active processing demands are imposed, TD + ADHD can be classified either as a phenotype expression of TD (Yordanova et al. 1996) or ADHD (Rothenberger et al. 2000), or as a unique nosology consistent with the interactive model for TD + ADHD (Yordanova et al. 1997; 2006). Together, these results show that the specification of TD + ADHD comorbidity depends on the level at which psychopathological conditions are evaluated. Basic cerebral functions in TD + ADHD coexistence, such as the sleep-wake or cortical excitability and inhibition, appear to be guided by independent TD- and ADHD-related pathogenic sources. Yet, any cognitive activation involving these basic functions, such as focused expectation, uncertainty control, or early selective attention (Yordanova et al. 1996; 1997; 2006), may lead to a complex interplay of the separate pathogenic sources, which may result in highly specific neurocognitive modes of information processing in comorbid patients. At the psychometric level, behavioral parameters during neuropsychological assessment and symptom expression during clinical assessment represent the most complex stage of integration where new markers of comorbidity may emerge as either isolated or bridging characteristics.

This multi-level scheme of comorbidity interpretation (Yordanova et al. 2006) shows that the definition of *symptom space* may not be limited to the psychometric domain (Cramer et al., target article), as it strongly depends on the level of organization at which the functioning of the neural substrate is quantified. Accordingly, the psychometric domain represents just one: the most fused and integral plane across a "vertical" scale where multiple "horizontal" planes of neurostructural organization exist to produce level-specific quantifiers, from molecular and neurogenetic to neurocognitive and psychometric (Fig. 1).

With this account, the network perspective proposed by Cramer et al. can be extended in the following directions:

1. The network approach may encompass phenotypes at separate levels of neurofunctional organization. Overlapping and non-overlapping signatures can be extracted at each level. Disclosing level-related direct associations may not only refine comorbidity specification, but also provide important information about underlying neural mechanisms.

2. As a further extension, a broader phenotype space can be constructed to expand the definition of *symptom space*. Multilevel quantifiers, rather than single-level (e.g., psychometric) signatures, can be included in statistical network evaluation. The multidisciplinary perspective stressed by Cramer et al. can certainly consider signatures derived from genetic, neurofunctional, neuroimaging, morphometric, neurotransmission, and such like, domains.

3. Constructing an integrated multi-level and multiple-domain phenotype space of signatures may enable the assessment of causality and relationships among different, yet interdependent, levels. Enlarged space entities can be analyzed in the framework of linear system concepts and methods. Importantly, nonlinear dynamic methods would extract cross-level interactions as integral descriptors of the behavior of a complex dynamic system (Rosso & Masoller 2009; Rosso et al. 2001).

A unique level-integrating principle for creating a multi-level phenotype space is provided by the concept of *neuroelectric oscillations*: Oscillatory signals are recorded in various brain structures (Başar et al. 2001; Buzsáki & Draguhn 2004). The temporal and spatial synchronization of frequency-specific oscillatory networks subserves information-processing mechanisms (Varela et al. 2001). Slow-frequency oscillations from the delta, theta, and alpha frequency bands have been associated with large-scale networks of executive and cognitive processing, and fast-frequency oscillations from the beta and gamma frequency bands have been related to local processes resulting also from neuronal firing (Gray & Singer 1989; Kirov et al. 2009; Sarnthein et al. 1998; von Stein & Sarnthein 2000). Oscillatory networks thus reflect neural functioning at different levels of organization of the neural substrate. Importantly, the synchronization of frequency-specific networks may be interdependent (Tort et al. 2009) and is also strongly modulated by the spontaneous multiple second-state variations of the default mode networks (Raichle et al. 2001). Neuroelectric oscillations have provided important markers of different mental disorders (e.g., Herrmann & Demiralp 2005) as well as comorbid conditions (Yordanova et al. 2001; 2006) and have promoted relevant models of child psychiatric disorders (Rothenberger 2009; Sonuga-Barke & Castellanos 2007). The relationships and dynamics of neuroelectric oscillations can therefore provide an integrating principle for the formation of multi-level space phenotype signatures, which may have a direct practical application for the identification and treatment of psychiatric disorders.

The abandonment of latent variables: Philosophical considerations

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Abstract: Cramer et al.'s critique of latent variables implicitly advocates a type of scientific anti-realism which can be extended to many dispositional constructs in scientific psychology. However, generalizing Cramer et al.'s network model in this way raises concerns about its applicability to psychopathology. The model could be improved by articulating why a given cluster of symptoms should be considered disordered.

From the force fields and potential energy of physicists to the traits, temperaments, and abilities of psychologists, making dispositions into something real is deeply entrenched in science. What is radical about re-thinking the scientific validity of latent variables is that they are contemporary proxies for dispositions. Latent variables are omnipresent in contemporary psychology, and dispositions even more so.

I agree with Cramer et al. that psychiatric comorbidity refers to a real, important phenomenon that should not be dismissed as an artifact of the classification system (Zachar 2009). For example, epidemiological research in the United States indicates that in any given year a majority of psychiatric disorders occur in only 14% of the people (Kessler et al. 1994). This 14% likely represents a *vulnerable population*. How should we model this vulnerability? One current view is that neuroticism, a historically important latent variable in scientific psychology, is a primary risk factor for psychopathology (Clark 2005; Kahn et al. 2005; Mineka et al. 1998; Rothbart & Ahadi 1994).

According to Cramer et al., however, the reality of a symptom pattern is not found hidden behind the symptoms, but in the symptoms themselves. They argue that symptoms are not effects of disorders, but rather, that relations between symptoms constitute disorders. This claim resembles the classical empiricists' contention that we have no knowledge of an underlying substance called *matter*, that is, what we know are observable properties only (color, hardness, etc.).

Given that latent variables are proxies for unobservable dispositions, the conceptual model described by Cramer et al. can be usefully applied to many hypothetical constructs in psychology, whether or not they are confirmable as latent variables. Exploring this a bit further can shed some light on what is being claimed about psychiatric disorders. Let me, therefore, briefly consider what the model might say about *basic emotions theory*, specifically, the non-essentialist model of James Russell (2003; 2008).

Russell is an anti-realist about affect programs in the same way that Cramer et al. appear to be anti-realists about latent variables. According to Russell, an emotion such as fear represents a family of states that have varying degrees of similarity to one another. Russell claims that different tokens of fear share overlapping components, but there is no set of components that all episodes of fear must share. Two or more episodes classified as fear could potentially have very few components in common. In philosophical terms, fear components such as raised eyebrows and elevated blood pressure are not manifestations of a natural kind; rather, they are individual events that happen to co-occur in ways that we have learned to notice. If scientists could account for all the mechanisms that explain the different parts of an emotional episode, says Russell, there would be no need to posit an additional mechanism called the *affect program* to explain the emotional episode itself.

Affect programs, like latent variables, are constructs that are attributed ontological significance. Why? Because it is important to account for the patterning that occurs, and affect programs fill that role. They are similar to what Medin and Ortony (1989) call *essence placeholders*. The key point for Russell is that the affect program model commits us to a false ontology. If we continue to use this ontology, we are not going to discover adequate scientific explanations of emotional phenomena. We need a better ontology. Similar to Cramer et al.'s claims about latent variables, Russell would prefer to eliminate the construct of affect programs from our scientific ontology, and with it the notion of basic emotions as legitimate scientific kinds.

One of the difficulties readers have with accepting Russell's model is that they expect the familiar categories of emotion to have some validity. They are uncomfortable with the possibility there is nothing more substantial about the patterns we do notice than those we do not notice. As a type of *causal non-essentialism*, Cramer et al.'s network model would allow that the patterning of emotion components occurs in a non-arbitrary way, but the patterning is best explained with reference to direct

causal connections between those components rather than with reference to unobserved affect programs. It could support the elimination of affect programs, but unlike for Russell, Occam's razor would not be applied to basic emotions as well. Perhaps basic emotions can refer to clusters that have a greater probability of spontaneously emerging from the dynamic interaction of causally connected components – in the same way that amino acids are reliably folded into proteins without benefit of a latent protein-folding mechanism that makes it occur.

The difference between emotions and psychiatric disorders is that we do not typically think that psychiatric disorders emerge spontaneously like everyday psychological states emerge – disorders entail a *failure* of a normal mechanism (Wakefield 1992). This is an important point because Cramer et al.'s argument is broader than the claim that shared symptoms, not latent variables, are the important causal factors in comorbidity; they also use relations among symptoms to explain psychiatric syndromes in general.

Perhaps the most important development in psychiatric classification in the last 20 years is the effort by many clinical psychologists and some psychiatrists to replace Robins and Guze's (1970) categorical approach to the medical model with a psychometrically based dimensional model (Livesley 2003; McCrae 1994; Watson 2005). What are the implications for the bold claim that latent variables (categorical or dimensional) are an inadequate basis for a science of psychopathology? For better or worse, success would mean that the network model might be a candidate for a new general model of psychopathology.

How does such a model fare as a general model of psychopathology? As currently formulated, the network model demarcates psychopathology as the collection of symptoms that are manifest in whatever psychiatrists decide to treat. Cases are defined when enough symptoms of the right type are present. This may be a bit too nominalistic. For example, what if psychiatrists start conceptualizing liberalism as a mental disorder – as some have suggested (Rossiter 2008; Savage 2005)? What resources would exist for not including the symptoms of liberalism in the total psychiatric symptom space?

In the latent variable model, the pathology is supposedly located in the hidden reality behind the symptom patterns. If there is no reality behind the symptom patterns, would "pathologies" be relocated in the symptoms themselves? Could psychopathology be an emergent property? Such a radical relocation project raises a list of interesting complications. Latent variables can be taken as proxies for the underlying pathological processes of the medical model, but justifying the reality of emergent pathologies would require a different kind of thinking.

Authors' Response

Complex realities require complex theories: Refining and extending the network approach to mental disorders

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Abstract: The majority of commentators agree on one thing: Our network approach might be the prime candidate for offering a new perspective on the origins of mental disorders. In our response, we elaborate on refinements (e.g., cognitive and genetic levels) and extensions (e.g., to Axis II disorders) of the network model, as well as discuss ways to test its validity.

R1. Introduction

In our target article, we have proposed a network view of mental disorders, in which systematic covariation between symptoms is explained by direct relations between the symptoms themselves. The approach breaks radically with the dominant doctrine, in which disorders are considered to be common causes of their symptoms (i.e., the *latent variable perspective*). We were pleased to see that many commentators view the *network approach* as a potential substantive theory of mental disorders. Given the varied set of responses, many of which proposed worthwhile empirical research suggestions and theoretical extensions of the approach, we have fortunately succeeded in bringing together researchers from different fields to reconsider what disorders are and how we should investigate them.

One of the most surprising and noteworthy facts about the present set of commentaries concerns what they do *not* contain: Very few commentators attempt to defend the received view that underlies many current approaches to psychopathology: that is, the latent variable perspective. We take this to imply that the time is ripe for a change of perspective. In addition, the comments have strengthened our conviction that, with the necessary refinements and extensions, "'inference to the best explanation" could ultimately lead us to the network approach as *the* substantive theory of mental disorders (Haig 2009). Certainly, **Rothenberger, Banaschewski, Becker, & Roessner** (**Rothenberger et al.**) argue that the network approach is complex with its "manifold interactions between symptoms," but we agree with them even more that this reflects reality. And as we will argue here, complex realities require complex theories.

In this response, we discuss the most important extensions, refinements, investigative tools, and objections voiced by the commentators according to the following themes. First, several commentators argued that network models can and necessarily must include latent variables (e.g., **Haig & Vertue**; **McFarland & Malta**). In section R2, we explain why some relations qualify for such a measurement model – and are thus likely to be incorporated into a network model – while others do not (e.g., depression as common cause of a cluster of symptoms). Other commentators provided excellent suggestions for refinement of the network model in order to include genetic, neurological, and cognitive levels of explanation (e.g., **Rubinsten & Henik**; **Yordanova, Kolev, Kirov, & Rothenberger** [**Yordanova et al.**]), which we discuss in section R3. Additionally, in section R4, we discuss ways to test the network model, as suggested by several commentators (e.g., **Davis & Plomin**; **Fleeson, Furr, & Arnold** [**Fleeson et al.**]; **Van der Sluis, Kan, & Dolan** [**Van der Sluis et al.**]). Section R5 investigates the possibility of extending the network approach to other disorders (e.g., Axis II personality disorders [**Bornstein**; **Ross**]). Section R6 focuses on an important question, posed by several commentators, as to what constitutes a mental disorder (**Haslam**; **Hood & Lovett**; **Zachar**).

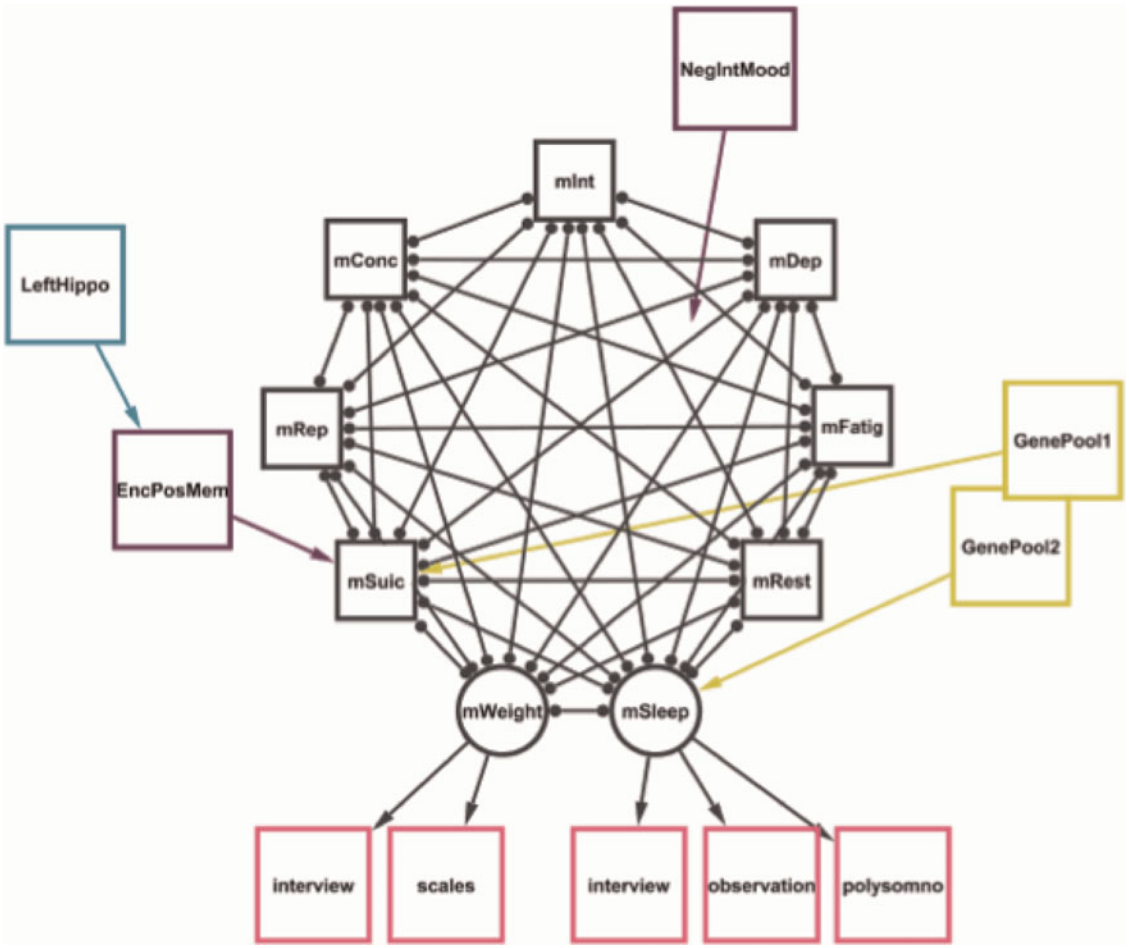

Figure R1. A hypothetical network model for major depression. *Circles* represent latent variables, and *squares* represent observed variables. The nine symptoms of major depression are represented as *dark gray squares/circles*. The *pink squares* represent multiple measurements for latent symptoms (i.e., weight and sleep problems in this example; see sect. R2). The *purple squares* represent the cognitive level of the model, the *blue square* the neurophysiological level, and the *yellow squares* the genetic level. Abbreviations key: *mInt*, loss of interest; *mDep*, depressed mood; *mFatig*, fatigue; *mRest*, restlessness; *mSleep*, sleep disturbances; *mWeight*, weight problems; *mSuic*, (thoughts of) suicide; *mRep*, self-reproach; *mConc*, concentration problems; *polysomno*, polysomnography; *EncPosMem*, problems in encoding/retrieving positive autobiographical memories; *NegIntMood*, negative interpretation of bad mood; and *LeftHippo*, smaller volume of the left hippocampus.

Finally, commentators raised methodological objections that claimed either to invalidate the network model we suggested (e.g., **Danks, Fancsali, Glymour, & Scheines** [**Danks et al.**]; **Krueger, DeYoung, & Markon** [**Krueger et al.**]), or to sustain a common cause view on mental disorders (e.g., **Belzung, de Villemeur, Lemoine, & Camus** [**Belzung et al.**]; **Humphry & McGrane**). In section R7, we discuss these issues and argue that – despite methodological difficulties that have to be addressed in the future – the network model should be viewed as the prime candidate to elucidate the origins of mental disorders.

R2. Latent variables in the network approach

Markus and **Molenaar** remark that, if the network approach is to move from a mere representation of the data to a possible representation of the underlying causal and functional relations between its components, one requires a way to deal with the fact that the observations (i.e., symptom reports) are likely to be imperfect indicators of these components (i.e., the actual symptoms). These commentators note that, if measurement error is neglected, relations between symptoms can be inaccurately represented because of attenuation effects. The only way to deal with this is to invoke latent variables into the model. Other commentators express this concern as well when discussing symptoms that should be measured in multiple ways (**Krueger et al.**; **McFarland & Malta**) or non-symptom causal processes that mediate the direct relations between symptoms (**Belzung et al.**; **Danks et al.**; **Haig & Vertue**; **Humphry & McGrane**). Our response is simply to acknowledge that this is the case; in fact, in our target article, we specifically hint at this idea in the last paragraph of section 4.

We construct the situation as follows: At the level of individual symptoms, we take symptom reports to be measures. If measurement error is to be accounted for at this level, one would indeed need multiple indicators

per symptom and a parallel extension of the network model with latent variables; for example, a network model for depression could include sleep disturbances as a latent variable measured with three observable indicators (i.e., clinical interview, polysomnography, laboratory observation; see **McFarland & Malta**). Figure R1 depicts such a network model with sleep disturbances and weight problems as latent variables. Also, a model in which some non-symptom causal processes are latent because they are measured in multiple ways (e.g., "major life events" for depression) is easy to conceive, and we welcome the development of such extensions of the model (**Belzung et al.**; **Danks et al.**; **Haig & Vertue**; **Humphry & McGrane**).

The central tenet of our target article is, therefore, not to shun latent variables completely. For example, a measurement model that includes a latent variable makes perfect sense in case of the symptom "insomnia" with three indicators. This is because (1) a natural referent exists (i.e., not falling asleep/not staying asleep), of which we know (2) how it affects our three measurements (e.g., trouble with falling asleep will be measured as a long time lying awake before falling asleep for the first time during a nightly observation in the laboratory); and we know (3) that it explains the correlation between the three measurements (i.e., the common cause of measures obtained in a sleep laboratory and of ticking the box "long time to fall asleep" in a questionnaire).

In case of mental disorders, on the other hand, a latent variable model is an unlikely candidate for giving a truthful explanation of the associations between distinct symptoms of a disorder. In other words, we do not object to measurement models per se, but to the idea that the association between a mental disorder and its symptoms is one of measurement. First, many supposed latent variables in psychological science – such as depression or neuroticism – do not appear to have a natural referent (for an extensive elaboration on this point, see Borsboom et al. 2009a). Second, without a natural referent, we have no idea how the supposed measurements would be affected by the latent variable, and we therefore cannot justify a common cause interpretation, where the disorder explains correlations between its symptoms. Thus, the things that render the relation between insomnia and three observed variables one of measurement are lacking in the case of, say, depression. Naturally, if one day we should find a natural referent for the hypothetical construct "depression," and we could prove that referent to be the common cause of all depression symptoms, the network model would be disproved. But we doubt that day will ever come.

R3. Refining the network approach: Genetics, brain, and cognition

The network model in our target article is, naturally, not the end of the story (**Ross**). To the contrary, the network we presented for comorbidity between major depression and generalized anxiety represents a starting point. Refining this model in particular – and the network idea in general – should be the focus of future research in order to adequately (1) test the validity of the model and (2) generate hypotheses about the etiology of particular mental disorders (**Johnson & Penke**).

Johnson & Penke correctly state that an important goal of the network model is to help unravel the etiology of a wide variety of mental disorders. We acknowledge that a plethora of work has already been done in that regard, but, as we also argued in our target article, that work might be grounded in the wrong psychometric theory of mental disorders. As such, *etiology* is currently interpreted in terms of the development of a single vulnerability (i.e., the common cause) that causes a cluster of symptoms. For example, an evolving lack of serotonin may be hypothesized to cause the symptoms of major depression. However, if a network approach, rather than a latent variable model, correctly describes the system, the conceptualization of etiology and vulnerability radically changes, for we are no longer talking about one, but about a multitude of vulnerabilities at the genetic, neurological, and cognitive levels that may explain the onset of symptoms and the relationships between them (**Fleeson et al.**; **Hyland**; **Rubinsten & Henik**; **Yordanova et al.**). Figure R1 depicts such a hypothetical descriptive network model for the nine symptoms of major depression. The etiology may then be conceptualized in terms of the development of such a network over time; naturally, this process may differ over individuals.

Many mental disorders have a strong *genetic* component, as evidenced by high heritability estimates, but, despite numerous research efforts, the genetic culprits have not been found (**Van der Sluis et al.**). This poses a dilemma. Are the heritability estimates wrong – and is the genetic influence on mental disorders hence highly exaggerated – or is there something wrong with the methods we use to investigate this issue? Van der Sluis et al. suggest the latter and corroborate this by referring to the practice of correlating genes to the entire aggregate of symptoms. If the network model is accurate in describing the origins of mental disorders, this method provides limited prospects for success in gene hunting. Since, in this case, there simply is no common cause, its hypothesized proxy (i.e., a sum score) is an amalgam of distinct factors and will only capture the genetic components that are shared by the aggregated symptoms and relations between them. As we have argued in our target article, it is likely that different genes (or constellations of genes) influence different symptoms (and relations between them). For instance, it is not a wild guess to assume that the symptoms "sleep disturbances" and "thoughts of suicide" are controlled by a different set of genes (with some overlap; see Fig. R1). Multiple genes for each symptom separately does render the entire picture far more complex, and we agree with Van der Sluis et al. that the network model faces a challenge in that regard. Part of this complexity could possibly be tackled by examining the time series of symptom development and relating the patterns that emerge from such analyses to (constellations) of genes.

While we generally reject the idea of one common cause underlying a constellation of symptoms, we by no means dismiss the potential relevance of pathological mechanisms discovered by the quest of finding such causes. For example, a smaller left hippocampal volume has been consistently found in people with major depression (e.g., see Bremner et al. 2000). Although it appears unlikely that this mechanism causes all depression symptoms, it could be one of the vulnerabilities underlying one or more symptoms; for instance, thoughts of suicide (see Fig. R1). Also

at the *neurological* level, **Rubinsten & Henik** argue that deficiencies along the intraparietal sulcus (IPS) – commonly associated with numerical cognition – are the common cause of the symptoms of developmental dyscalculia (DD). Although we agree that the evidence points to the relevance of IPS deficiencies, we are not so sure that those deficiencies are the common cause. Since DD involves deficiencies in a variety of complex abilities that require input from memory, attention, and spatial systems, a single underlying vulnerability is highly unlikely (e.g., see Cohen Kadosh & Walsh 2009; Landerl et al. 2004). Thus, also in the case of DD, existing neurophysiological findings can be incorporated easily into a network perspective once one is willing to accept the demise of the "common cause" idea.

At the *cognitive level*, it is, for instance, well known that both major depression and generalized anxiety are intimately connected to negative beliefs, as is evidenced by the success of cognitive therapy in reducing depression and preventing relapse (DeRubeis et al. 2005; Kuyken et al. 2008; Papageorgiou & Wells 2001; Paykel et al. 1999; Wells & Carter 2001; see also **Hyland**). We are skeptical about Hyland's view that those beliefs form an interconnected system that completely explains the onset of depression and/or generalized anxiety. Rather, we hypothesize that negative beliefs directly influence (1) symptoms – for example, negative thinking that causes a depressed mood; and (2) relations between symptoms – for example, an overly negative interpretation of one's depressed mood that results in making a suicide plan (see Fig. R1). **Staniloiu & Markowitsch** report another intriguing possibility: Problems in encoding and retrieving positive autobiographic memories could result in an inability to imagine an optimistic future, which may lead to the onset of the symptom "suicide attempt" (Markowitsch et al. 2003; Schacter & Addis 2009; Sharot et al. 2007).

R4. How to investigate the network model? A research agenda

We have provided several arguments for the thesis that a network model paints a more realistic picture of mental disorders than the latent variable model does. Naturally, future research must determine whether the network model is also the better theory in reality, and several commentators have put forward some excellent suggestions for a research agenda (e.g., **Davis & Plomin**; **Fleeson et al.**; **Tzur-Bitan, Meiran, & Shahar** [**Tzur-Bitan et al.**]). Given the complexity of the network approach, such an agenda is necessarily comprehensive. As such, when **Krueger et al.** ask, "How would one use the information in Figure 4 to explain to a policy maker how we might go about spending public funds wisely in the service of working to ameliorate the burden of depression and anxiety? By funding hundreds of separate projects focused on understanding each line in the figure?" – our short answer is yes. For those skeptical of this answer, we suggest that the same question may be asked about, say, complex systems like the earth's climate. Should we really fund hundreds of projects investigating the diverse factors that influence climate change? The answer to that question is uncontroversially affirmative, and it has not proven difficult to persuade policy makers of this fact. We do not see why the situation would be different for mental disorders. Given this perspective, we think of three lines along which network research should ideally be aligned: (1) validating the network model, (2) elucidating the vulnerabilities underlying (relations between) symptoms (see also **Fleeson et al.**) and (3) tracking the developmental trajectories of symptom constellations.

R4.1. Validating the network model

Relations between symptoms represent an ideal opportunity to test the network model against the latent variable model: If no latent variable exists, one should find that experimentally manipulating one symptom results in change in another symptom. Some work has already been done in that regard; for example, unsurprisingly, one look at the literature reveals a direct effect of sleep deprivation on fatigue (e.g., see Durmer & Dinges 2005). Other symptom relations, such as the one between loss of interest and worrying about multiple events in Figure 4 of our target article, appear less obvious and need experimental verification in the future. In a more indirect manner, the network model could be confirmed by the genetic association studies (GAS) on the individual symptoms, as proposed by **Van der Sluis et al.**; it would be especially interesting to execute such analyses on patterns found in time series that describe symptom dynamics. If the network model is true, this type of GAS should reveal constellations of genes that better account for the high heritability of mental disorders than GAS on a sum score. In the same vein, **Davis & Plomin** suggest multidimensional scaling as a method to reveal the genetic closeness of multiple symptoms. If such endeavors would point to the presence of direct relations between symptoms, the latent variable model could be put to rest in psychopathology.

R4.2. Elucidating vulnerabilities

Fortunately, there may be no need for funding "hundreds of projects," as **Krueger et al.** fear, since many of such projects, aimed at understanding the inner workings of a variety of symptoms, have already been carried out; most symptoms in Figure 4 of our target article are associated with large scientific literatures (e.g., fatigue, anxiety). With regard to vulnerabilities underlying the relations between symptoms, not all edges are an a priori mystery to us; for example, the mechanisms that are involved in the influence of sleep deprivation on fatigue are well known (e.g., see Durmer & Dinges 2005).

With regard to symptom relations whose underlying mechanisms are less well-known, insights from treatment rationales should further our understanding. For instance, mindfulness-based cognitive therapy offers a specific hypothesis with regard to the relation of depressed mood with the other symptoms of depression: Depressed mood triggers ruminative thinking, which – if not hindered by a successful intervention – could lead to other depression symptoms (e.g., see Ma & Teasdale 2004; Nolen-Hoeksema 2000; Segal et al. 2002). Another example comes from the panic disorder literature in which renewed interpretation of bodily signals is used to break the link between having a panic attack and worrying

about its consequences ("I will have a heart attack"; e.g., see Clark et al. 1994). On a related note, several successful interventions are not primarily aimed at reducing or eliminating symptoms or the relations between them but, rather, at reinforcing so-called protective factors. For example, the relative success of the methadone program is attributable to reinforcing coping skills and finding work and housing (i.e., protective factors) while stabilizing the addiction with the methadone. Once a stable situation is created, addicts enter a total abstinence program (e.g., see Gossop et al. 2002; Van den Brink et al. 1999). Such treatment programs could provide some valuable insights into the mechanisms by which one progresses from a disordered to a healthy state.

R4.3. Tracking developmental trajectories

Much of the current literature reports research that involves interindividual research, often carried out cross-sectionally. Although such research can provide important insights, **Wass & Karmiloff-Smith** correctly suggest that it results in a snapshot of reality: an interindividual picture of mental disorders, frozen at a particular time frame. In reality, it is likely that, for instance, edge strengths differ across individuals, as well as across time. If so, another line of research is required to generate answers to two pivotal questions: (1) How do mental disorders develop, and (2) how does that development differ across individuals (**Fleeson et al.**; **Rothenberger et al.**). Such variations should be detectable through the intra-individual analysis of time series, as noted by various commentators (e.g., Fleeson et al.; **Tzur-Bitan et al.**; **Van Geert & Steenbeek**). In earlier times, it was quite difficult to obtain data suitable for such analyses. Fortunately, we now live in a time in which intensive time-series data can be gathered relatively easily (e.g., by letting patients report the status of symptoms through handheld devices, etc.). We think that, within a few years, it will become possible to analyze symptom development in real time, and to update network structures and parameters as the data come in. And when that time comes, we are confident that thorough investigation of the network approach will result in a better understanding of symptoms, their relationships, and their course in individuals over time.

R5. Extending the network approach to other disorders

In our target article, we introduced the network approach for two disorders that are prime examples of Axis I disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*; American Psychiatric Association 1994). Any theory that presents itself as *the* potential substantive theory of mental disorders must be able to explain more than comorbidity between major depression and generalized anxiety disorder (**Johnson & Penke**). As a first step, we deem it necessary to evaluate to what extent the network approach fits a variety of other mental disorders (also see **Cervone**).

With regard to other Axis I disorders, some commentators have presented specific examples of (clusters of) disorders for which common causes are supposedly identified, thereby rendering the network approach invalid in those cases (e.g., **Ross**; **Rubinsten & Henik**). For example, Ross argues that addictions share a common cause: namely, hyperactivation of the dopamine reward circuit combined with weakened frontal and prefrontal serotonin and gamma-aminobutyric acid (GABA) circuits. We share Ross's view on the importance of these brain pathologies in addiction; however, we do not agree that such pathologies automatically qualify as the common cause of addictions. The most commonly reported consequences of the dysfunctional dopamine, serotonin, and GABA circuits are (1) the strong desire to consume salient targets, coupled with (2) difficulty resisting that desire. In other words, the brain pathologies that Ross mentions result in the *core characteristics* of an addiction. However, does this make those brain pathologies the *common cause* of addiction? To qualify as such, those pathologies should *also* cause the other symptoms of addiction. This is unlikely.

If we take a look at the *DSM-IV* criteria for substance abuse, for instance, we notice (1) the apparent inability of dysfunctional neurotransmitter circuits to explain "recurrent substance use *resulting in a failure to fulfill major role obligations*"; and (2) the undeniable possibility of direct relations between the symptoms of addiction: "Recurrent substance use in situations in which it is physically hazardous" (e.g., drunk driving) can cause "recurrent substance-related legal problems" (e.g., getting arrested for drunk driving). As such, we think addiction can potentially be envisioned as a causal chain of symptoms in which one symptom – desire to consume and inability to withstand this – may be triggered by dysfunctional dopamine, serotonin, and GABA circuits; thus, no common cause, but one pathological mechanism – in combination with other etiological factors – potentially results in a cascade of events in a network of addiction symptoms (i.e., the "fan-out" principle that **Wass & Karmiloff-Smith** mention). Such a chain of symptoms is also likely in panic disorder and other – very heterogeneous – Axis I disorders such as schizophrenia and attention-deficit hyperactivity disorder (ADHD). Hence, in these cases the network approach cannot be ruled out a priori (e.g., Borsboom 2008).

Considering the extension of the network approach to Axis II disorders, **Bornstein** sees some roadblocks that need to be overcome in the case of personality disorders (PDs). First, patients with PDs tend to experience their symptoms as congruent with themselves. As a result, those patients have limited insight into their own condition. Bornstein rightly sees two resulting consequences: (1) Self-report measurements alone will not be adequate in assessing people with suspected personality pathology, and (2) the symptoms that patients cannot reflect on themselves are in a sense "latent." However, we do not think these consequences pose serious problems for the network approach since – as we outlined in section R2 – it can easily deal with latent variables that have an established measurement relationship with a set of indicators, including tests that do not rely on self-assessment. Second, the revision of PD symptoms is founded on a desire to both increase diagnostic accuracy and reduce comorbidity. According to Bornstein (2003), this practice has resulted in simply removing symptoms from the diagnostic checklist, and, as Bornstein rightly claims, this poses

a potential problem for the network approach; however, not in terms of its potential as substantive theory of mental disorders, but in terms of its practical applicability to PDs with potentially incomplete symptom inventories. So, in the case of Axis II PDs, we see no immediate problems that the network approach cannot surmount.

R6. What is a mental disorder?

In our target article, we argued that boundaries between mental disorders are necessarily fuzzy. In contrast, **Haslam** argues that boundaries between categories of the same disorder (e.g., "disordered" versus "not disordered") are not fuzzy at all. To address this apparent dilemma properly, we dissect a disorder network in two components: (1) its structure and (2) its state. The *structure* of a disorder network refers to the strength of the relations between symptoms. As we show in Figure R1, those relations are controlled by a host of vulnerabilities (e.g., negative interpretation of one's mood resulting in a relatively strong relation between depressed mood and thoughts of suicide). Since those vulnerabilities probably differ across individuals, it is safe to assume that the resulting basic network structure is individually tailored as well. Now, pertaining to comorbidity, it is likely that, in some cases, individual network structures do not obey the *DSM* boundaries between disorders (nor any other fixed boundaries). It is likely, as well, that certain vulnerabilities influence relations between symptoms of different disorders: for instance, ruminative thinking may strengthen the relation between "depressed mood" and "chronic anxiety." As such, the boundary between major depression and generalized anxiety for someone with a ruminative thinking style probably (1) does not equal the *DSM*-defined boundary (because of a strong relation between "depressed mood" and "chronic anxiety") and (2) lies somewhere else than the boundary of someone without that thinking style. Thus, at the individual level, the line can be drawn practically anywhere and therefore we defend the notion of fuzzy boundaries in these cases. In other cases, a sharp boundary between two disorders might be more feasible; for instance, because relations between symptoms of these disorders are virtually nonexistent or negative. For example, large individual differences in the boundary between social anxiety and psychopathy are not very likely given the opposite nature of the symptoms of those disorders (e.g., "excessive self-consciousness and anxiety in everyday social situations" versus "grandiose sense of self-worth"; cf. Hare 2003).

The *state* of a disorder network depends on how much symptoms are "on." When adhering to a categorical perspective, disorder networks can be in two or more stable states. For example, with two stable states, one commonly distinguishes between a *healthy state*, in which few symptoms are "on," and a *disordered state*, in which several symptoms are "on." In these cases, a sharp boundary is needed to distinguish few from several. Now, we agree with **Haslam** that such sharp boundaries are theoretically possible and that evidence for two latent classes corroborates that hypothesis (provided that the analysis was conducted on a large and representative sample). However, as we already argued for a network's structure, it is unlikely that boundaries between states are invariant over persons; for, in subjective terms, some people feel depressed because they have sleep and concentration problems for two weeks, whereas others succumb to a full-blown depression only after a prolonged period of experiencing a multitude of symptoms. Therefore, in these cases, a more dimensional perspective might be in order; that is, no sharp boundaries between categories, but, instead, a continuum of network activation. Here, we think that symptom severity might be an excellent candidate for representing the degree of network activation (**Markus**): the more severe someone's symptoms are, the more that person is located toward the "disordered" end of the continuum.

In theory, any network with connected nodes (i.e., structure) that can be in different states could be taken to qualify as a mental disorder. As such, liberalism could be viewed as a mental disorder (**Zachar**): a set of connected political beliefs (e.g., if you believe in freedom of religion for everyone, then it is more likely that you are tolerant of minorities) that we call "liberalism" when a sufficient number of nodes are activated. In practice, though, we – and probably the majority of humankind with us – do not consider liberalism to be a mental disorder. Why? The *DSM* provides a sensible answer: The symptoms of any candidate mental disorder should cause "clinically significant distress or impairment in social, occupational, or other important areas of functioning" in the person who is experiencing those symptoms (American Psychiatric Association 1994). Although liberalism apparently causes distress in some *other* people (see Savage 2005), it clearly does not satisfy the *DSM*'s prerequisite. Thus, providing a sensible boundary between disorders and non-disorders, we would welcome this prerequisite as an extra node in the symptom space.

About 40% of people with major depression experience a new depressive episode after treatment (e.g., Paykel 2008). Any substantive theory of mental disorders must be able to explain such *recurrence*, a phenomenon that is very common in a host of mental disorders. In our opinion, the network approach is up to that task. Take, for instance, an alcoholic who, because of treatment, manages to stay sober, as a result of which the other symptoms of his or her substance abuse also subside. Also suppose that this person's network has strong connections between symptoms; that is, if one symptom turns on, it is likely that the other symptoms will turn on, as well. As such, we have a situation in which the substance abuse network is in a more or less *healthy* state (i.e., no symptoms are "on") while the structure of the network is *risky* (and thus unhealthy). Now, this situation is exactly what makes a disorder likely to recur: If, for whatever reason, this person decides to drink one beer, it will likely result in a cascade of symptoms being turned on, and eventually the network will return to a disordered state. In other words, recurrence is most likely when the healthy state of a disorder network is unstable because of the strong connections between its symptoms. We think this is precisely what clinicians mean when they talk about silent disorders, and therefore we do not agree with **Hood & Lovett** that the network approach cannot accommodate such notions. On a final note, in the case of major depression, it is established that one of the most reliable predictors of recurrence is the presence of residual symptoms (e.g., Kennedy & Paykel 2004). But we also know that not every patient with residual

symptoms experiences a subsequent recurrence. If we are right in suggesting that recurrence is most likely when the structure of the network is strong, residual symptoms in depression patients offer a way to prove this hypothesis: Of patients with residual symptoms, only those with strong connections between symptoms should eventually experience a new episode of major depression.

R7. Networks versus common causes: Methodological issues

Several commentators raise methodological issues regarding the network approach as opposed to latent variable models. In the following, we discuss criticisms according to the methodological topics mentioned by the commentators.

R7.1. Local independence

Many commentators question our criticism of the local independence assumption. In their opinion, a unidimensional model with local independence is unnecessarily strict (e.g., **Humphry & McGrane**; **Markus**; **Molenaar**). It is true that violations of local independence can be represented in a latent variable model, for instance, by allowing correlated residuals or direct relations between indicator variables. However, these modeling possibilities should not be given too much conceptual weight. Being more than a convenient restriction, local independence has the status of an axiom in measurement models used in psychometrics (e.g., Ellis & Junker 1997; Holland & Rosenbaum 1986; Junker & Sijtsma 2001). This makes sense because psychometric models aim to give conditions under which composite scores (e.g., summed item scores) can be treated as measures of a latent variable. A prerequisite for this is that the item scores measure the same latent variable, which plausibly requires that the latent variable functions as a common cause; and the classical way of testing this is by testing whether the latent variable screens off the associations between the item scores. This is precisely what local independence requires. Thus, although it is statistically possible to allow for direct relations between indicator variables in a model, this should be considered a deviation from a psychometric norm (which in itself is reasonable in setting up a measurement model). As such, a unidimensional model with local independence is anything but a "straw man" (**Danks et al.**).

R7.2. Model equivalence

Several commentators raise the possibility that we may have overstated the difference between networks and latent variable models. **Danks et al.** note that cyclic graphs and latent variable models are closely related; **Molenaar** points to the fact that longitudinal factor models are equivalent to specific types of directed network models; and **Humphry & McGrane** indicate that latent variable models concern individual differences and, as such, may allow for individual level causal relations without violating the individual differences model.

It is true that latent variable models and network models are statistically indistinguishable in certain situations. A prominent example of such an exact indistinguishability is the mutualism model of intelligence proposed by Van der Maas et al. (2006), which is a network model that can produce data that are exactly equivalent to a single factor model. Similar relations are likely to exist for item response theory (IRT) models; **Molenaar**, in earlier work (see Molenaar 2003, p. 82) has noted the close relation between Markov field models, such as the Ising model, and IRT models like those of Rasch (1960) and Birnbaum (1968). Indeed, one supposes that model equivalence may obtain as well in those cases.

Does this render the network model and the latent variable model equivalent in general? No, because the inability to distinguish between different possible generating models in a given data-set does not imply that the models are equivalent with respect to all possible data-sets or under all possible interventions. Thus, the advice in a model equivalence situation is to get better data, such as intensive time series (see sect. R4).

R7.3. Parsimony

Krueger et al. defend the latent variable model by emphasizing its superior parsimony relative to the network approach. First, latent variable models are not *inherently* more parsimonious than network models because the number of parameters of the latter can be made arbitrarily small. For instance, suppose that one has k observed dichotomous symptoms. If one assumes a completely connected network consisting of bidirectional relations of equal size, where these relations are functionally the same for any two nodes (e.g., logistic relations with equal intercepts and slopes, as in a Boltzmann machine; see Ackley et al. 1985), then, statistically speaking, one has an extremely parsimonious model even though it may consist of many – namely, $k(k - 1)/2$ – connections between variables.

Second, it should be recognized that even though parsimony is a useful criterion in choosing between statistical models, it will lead to truth only if reality itself is simple; if this is not the case, then we may deceive ourselves by overemphasizing parsimony. As Tryon (1935, p. 428) remarked, "The 'law' of parsimony is not a natural law, but a rule agreed upon among men to simplify their thinking." While simplifying our thinking is clearly useful in scientific investigation, complex realities will ultimately require complex models. In the case of mental disorders, we doubt that reality is simple given the likelihood of variation in network structure over individuals and time. As such, an extremely restricted model such as a Boltzmann machine – although favorable in terms of its parsimony – might not be particularly viable. Therefore, we think that the sword of parsimony should be wielded with caution, for we may accidentally kill promising candidate models through its use.

R7.4. Extensions of the network approach

Danks et al. provide one of the most critical analyses of our approach. First, they raise a number of questions concerning terminology and procedure. For instance, they criticize our use of the term *centrality* because "[centrality] is neither a causal nor a statistical notion." This is obviously correct; it is a notion that comes from network analysis

and has proved to be useful in many contexts (e.g., see Boccaletti et al. 2006). Danks et al. also question our statement that observables in a standard psychometric latent variable model are exchangeable. In a measurement model, observables do not differ with respect to the property they measure; they are thus exchangeable in this sense. And it is this exchangeability that – among other things – renders the standard measurement model inappropriate in the context of psychopathology, for how could "weight loss" measure the same property as "suicide plans"?[1] Finally, Danks et al. indicate that the data we analyzed involved a great amount of missingness. We agree but refer to Note 6 of our target article, where we highlight an appropriate estimation approach we used to deal with the data, which is missing at random because of the skip structure of the interview schedule used in the National Comorbidity Survey Replication (NCS-R).

Second, **Danks et al.** state that we "do not engage what is known" about the investigation of causal relations, instead settling for an unsatisfactory and unrestrictive visualization method. They propose that causal inference algorithms should be used instead and report the outcome of an algorithmic search procedure. Perhaps ironically, the use of such procedures formed the starting point of our research. However, the search procedures as implemented in the program TETRAD (Scheines et al. 1996) returned causal structures that we felt were extremely hard to make sense of. This is also the case for the model suggested by Danks et al., in which, for instance, the core symptoms of depression and generalized anxiety (i.e., depressed mood and anxiety) are completely disconnected from the model. Our diagnosis of this situation is that two assumptions of the search algorithms in existence are not satisfied in the data at hand: (1) Individuals have the exact same causal structure and (2) resulting graphs are acyclic. In contrast, we think that the network structure of mental disorders (1) varies over individuals and (2) likely contains feedback loops. Therefore, we judge the implementation of causal search algorithms to be preliminary; it would be more sensible to gather time-series data on symptom dynamics and to fit models on an intra-individual basis. However, what we can do unproblematically, absent such intensive time-series data, is to provide a starting point for further investigations and hypothesis formation, based on the visualization of statistical associations that exist in the data, and this is what we aimed to do. This does not commit us to any particular type of modeling, while it serves the purpose of introducing and explaining the network approach extremely well. In conditions that justify their use, however, we acknowledge that causal modeling and search algorithms may be very useful.

NOTE

1. The exchangeability of items with respect to the property they measure is clear from the fact that one can parameterize, for instance, standard IRT models such as the one- and two-parameter logistic models by identifying the latent variable with the expectation of any one of the item responses (Gunter Maris, personal communication). A similar situation holds for the (essentially) tau-equivalent model of classical test theory (Lord & Novick 1968), in which the expectations of observed variables are simple transformations of one another, and for the congeneric model of factor analysis, in which the observed variables are linear transformations of one another (Jöreskog 1971). Intuitively, this means that if one has a single perfect thermometer, adding information from other, noisy thermometers is useless (note that this makes sense in a measurement situation). In contrast, if one knew the expectation of the item "how much weight have you lost?" one would presumably still want to know whether the person had suicide plans.

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[The letters "a" and "r" before author's initials stand for target article and response references, respectively.]

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