Network Analysis: An Integrative Approach to the Structure of Psychopathology

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Abstract

In network approaches to psychopathology, disorders result from the causal interplay between symptoms (e.g., worry → insomnia → fatigue), possibly involving feedback loops (e.g., a person may engage in substance abuse to forget the problems that arose due to substance abuse). The present review examines methodologies suited to identify such symptom networks and discusses network analysis techniques that may be used to extract clinically and scientifically useful information from such networks (e.g., which symptom is most central in a person's network). The authors also show how network analysis techniques may be used to construct simulation models that mimic symptom dynamics. Network approaches naturally explain the limited success of traditional research strategies, which are typically based on the idea that symptoms are manifestations of some common underlying factor, while offering promising methodological alternatives. In addition, these techniques may offer possibilities to guide and evaluate therapeutic interventions.

Contents

INTRODUCTION

Why is it that some people, from all walks of life, are vulnerable to developing mental disorders, while others seem to get through life's trials and tribulations relatively unscathed? Why are researchers unable to identify the essential characteristics of mental disorders, whether psychological, neurological, or genetic in character? What are mental disorders in the first place?

In contrast to the expectations that existed a century ago, when psychopathology research became an organized scientific enterprise, there appear to be no simple answers to these and other fundamental questions about the origins of psychopathology. The great unitary schools of thought in psychopathology research that tried to reduce mental disorders to simple psychological, environmental, or biological dysfunctions or predispositions have all tripped over the massively multifactorial etiology of these disorders (Kendler 2005a, Nolen-Hoeksema & Watkins 2011, Zachar & Kendler 2007). For example, in recent years, many had hoped to identify neatly separated gene sets that cause certain mental disorders. However, it turns out that "genes do not read DSM-IV" (Stefanis 2008): Despite the moderate heritability of many disorders, effects of particular genes on the risk for developing particular mental disorders are small and rarely, if at all, specific to these disorders (Kendler 2005b).

Intriguingly, however, despite the fact that disorders apparently have causes everywhere and nowhere, the symptoms of mental disorders do create reliable patterns of covariance. That is, there must be something that makes a symptom of, say, major depression (MD) hang together more strongly with another symptom of MD than with a symptom of, say, panic disorder (PD). What is that something?

The currently dominant answer to that question is "the disorder itself." Inspired by the successful paradigm of Western medicine (Hyland 2011), the disease model states that the problems that people encounter in life are "symptoms" of a reasonably small set of underlying "disorders" that cause these symptoms (analogous to a lung tumor, which causes shortness of breath, chest pain and coughing up blood). Thus, with this model in mind, the symptoms of MD hang together strongly because they are caused by the same underlying disorder, namely MD. It is exactly this kind of thinking that inspired the quest for psychological/environmental/biological essences of

mental disorders. And as we have seen, this quest has failed, and we interpret this failure as a falsification of the disease model in psychopathology.

We are not alone in questioning the appropriateness of the disease model for psychopathology: Most scholars agree that this currently dominant paradigm is problematic. It is, however, at present, unclear how we could free ourselves from it. This is because current handling of psychopathology data is predicated on traditional psychometric approaches that are the technical mirror of this paradigm. In these approaches, observables (clinical symptoms) are explained by means of a small set of latent variables, just like symptoms are explained by disorders. For example, in a latent variable model, PD is a latent variable that causes its observable symptoms, such as experiencing panic attacks. From this psychometric perspective, symptoms are regarded as measurements of a disorder, and in accordance, symptoms are aggregated in a total score that reflects a person's stance on that latent variable (Borsboom 2008a,b; Borsboom et al. 2003). Thus, the dominant paradigm is not merely a matter of theoretical choice, but also of methodological and pragmatic necessity: For the greater part of the scientific history of clinical psychology, the common cause idea—by which a common latent disorder determines a set of symptoms—was simply the only psychometric game in town.

However, there is now a new game in town, and it is called network analysis. In this review, we argue that complex network approaches, which are currently being developed at the crossroads of various scientific fields (Barabási 2011), have the potential to provide a way of thinking about disorders that does justice to their complex organization. In such approaches, disorders are conceptualized as systems of causally connected symptoms rather than as effects of a latent disorder. Using network analysis techniques, such systems can be represented, analyzed, and studied in their full complexity. In addition, network modeling has the philosophical advantage of dropping the unrealistic idea that symptoms of a single disorder share a single causal background, while it simultaneously avoids the relativistic consequence that disorders are merely labels for an arbitrary set of symptoms: It provides a middle ground in which disorders exist as systems, rather than as entities (see also Kendler et al. 2011).

We aim at explicating the basic theoretical premises of this network approach as well as offering a practical guide for how to collect and analyze psychopathological data with a network model in mind. Our goal is to allow interested readers to directly replicate our examples and apply them to their own data. Thus, all analyses are carried out on publicly available data from the National Comorbidity Survey Replication study (NCS-R; Kessler et al. 2004, 2005a,b) and executed using multiple freely available software packages that run in the free software statistical environment R (**http://cran.r-project.org**): igraph (Csárdi & Nepusz 2006), PcAlg (Kalisch et al. 2012), ppcor (Kalisch et al. 2012), and qgraph (Epskamp et al. 2012). Our R-code (available by following the Supplemental Materials link from the Annual Reviews home page at **http://www.annualreviews.org**) allows readers to replicate the analyses as they go along. The emphasis on free availability of data and replicability of the reported analyses occasionally means that the analyses may not be fully appropriate for the data (e.g., when computing partial correlations on dichotomous variables); in these cases, which will be indicated to the reader, the empirical results have the main purpose of illustration rather than interpretation in meaningful substantive terms. Before delving into statistics and data analysis, however, we first attack a central problem of current psychopathology research head-on: the erroneous but influential paradigm that symptoms are caused by disorders.

Supplemental Material

SYMPTOMS AND DISORDERS IN PSYCHOPATHOLOGY

Let us start with the facts. We know for certain that people suffer from symptoms (e.g., fatigue, insomnia, hallucinations, depressed mood) and that these symptoms cluster in a nonarbitrary

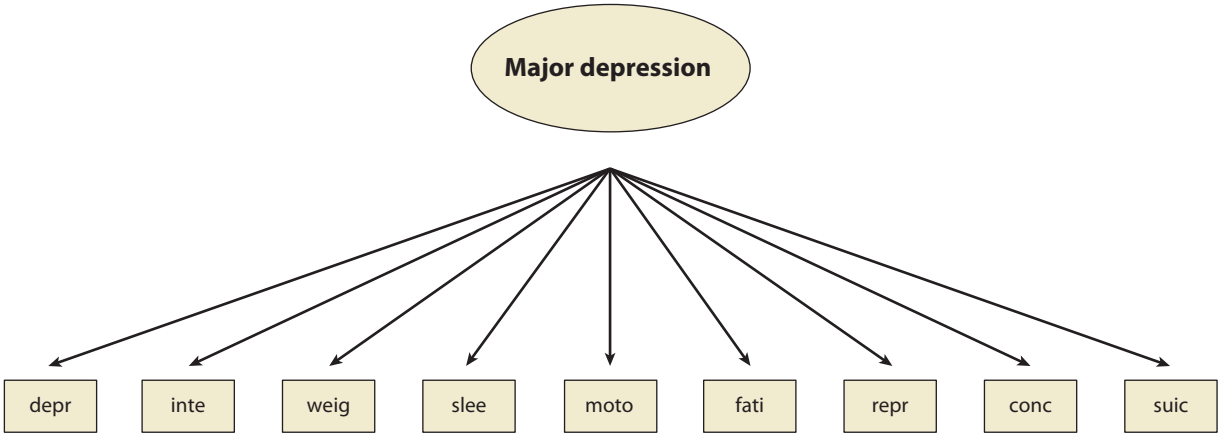

Figure 1

The relation between the disorder major depression (MD) and its observable symptoms according to a medical disease model. According to this model, MD (the oval at the top of the figure) is the root cause of its observable symptoms (the boxes at the bottom of the figure). Arrows point from the root cause (MD) to its observable symptoms, but not the other way around. See **Table 1** for definitions of abbreviated terms.

way. It is important to note here that for most psychopathological conditions, the symptoms [i.e., the problems as they are listed in diagnostic systems such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)] are the only empirically identifiable causes of distress. That is, mental disorders are themselves not empirically identifiable in that they cannot be diagnosed independently of their symptoms: There is no lab test for MD, PD, or schizophrenia as exists for, say, Down syndrome (i.e., identifying the presence of a third copy of chromosome 21).

It is useful to contrast the situation in psychopathology with that in medicine. Suppose one suffers from symptoms like headaches, forgetfulness, and foggy eyesight. These symptoms may be the result of a brain tumor. Such a tumor is an empirically identifiable entity that is conceptually separated from its symptomatic effects: One may have (*a*) headaches without a brain tumor and (*b*) a brain tumor without headaches. If the headaches are actually a symptom of the tumor, it is further the case that (*c*) one in fact does have headaches and a brain tumor, and (*d*) the headaches would not have been present without the tumor. Thus, in medicine, one can separate the medical condition from its symptoms [one can occur without the other; see conditions (*a*) and (*b*)] and one can identify the medical condition as the root cause of the symptoms [see conditions (*c*) and (*d*)]; as a result, it is usually beneficial to treat the root cause—in this example, removing the brain tumor. Much of the success of modern medicine is based on this disease model, which in fact could be argued to be the single most important idea in medical diagnosis as we currently know it (Hyland 2011).

Appearances suggest that, in psychopathology, an analogous process is at work. An example is presented in **Figure 1**, in which MD is the root cause of its observable symptoms (see **Table 1** for the accompanying legend). However, this similarity between psychopathology and modern medicine is only superficial. Certainly, clients are diagnosed with a disorder on the basis of a set of symptoms, after which the diagnosis is used to choose a treatment protocol. This suggests the identification and treatment of a root cause. However, although in the past decades much has been made of the suggestion that symptoms in psychopathology do have such root causes (variously suggested to have a basis in repressed desires, learned helplessness, hormonal imbalances, neural abnormalities, or genetic defects), it has so far been impossible to identify these empirically. In fact, it is impossible to identify any of the common mental disorders as conditions that exist

Table 1 Legend for Figures 1, 2, 4, 7, and 8

Abbreviation	Meaning	Belongs to disorder
depr	Depressed mood	MD
inte	Loss of interest	MD
weig	Weight problems	MD
moto	Psychomotor disturbances	MD
repr	Self-reproach	MD
suic	Suicidal ideation	MD
mSle	Sleep problems	MD
mFat	Fatigue	MD
mCon	Concentration problems	MD
slee	Sleep problems	MD/GAD
conc	Concentration problems	MD/GAD
fati	Fatigue	MD/GAD
gSle	Sleep problems	GAD
gFat	Fatigue	GAD
gCon	Concentration problems	GAD
anxi	Chronic anxiety/worry	GAD
even	Anxiety about >1 event	GAD
ctrl	No control over anxiety	GAD
irri	Irritable	GAD
musc	Muscle tension	GAD
edge	Feeling on edge	GAD

GAD, generalized anxiety disorder; MD, major depression.

independently of their symptoms. In our view, it is unlikely that this will change; that is, we consider it unlikely that somewhere in the future, with better detection equipment and larger sample sizes, we will be able to identify such conditions independently of their symptoms.

The reason that this is so unlikely is that, in order for a disease model to hold, it should be possible to conceptually separate conditions from symptoms; that is, it must be possible (or at least imaginable) that a person should have a condition/disease without the associated symptoms. For medical diseases, this is not only a conceptual possibility, but a commonly observed state of affairs: For example, a sizeable proportion of patients with lung cancer in its early stages do not report having any symptoms. For mental disorders, however, such scenarios are very unlikely: If MD were a condition that existed independently of its symptoms, then it should be possible to be depressed without feeling blue or disinterested (the core symptoms of MD as defined in DSM-IV). If PD were a separately identifiable disease, then it should be possible to have PD without experiencing panic attacks. If substance use disorder were a separately identifiable disease, then it should be possible to have this disorder without abusing a substance. These are situations so highly unlikely to occur that we propose to accept, if only as a working assumption, the proposition that mental disorders cannot be separated from their symptoms. As an important corollary, this means that disorders cannot be causes of these symptoms—at least, not in the way that tumors and bacterial infections are causes of symptoms in medicine. This strongly suggests that the treatment of disorders as causes that exist independently of the symptoms used to identify them involves an unwarranted reification (Hyman 2010).

Clearly, the relation between symptoms and disorders has to be conceptualized differently, not only because mental disorders are not identifiable as separate disease entities, but also because there appear to be many direct causal relations between symptoms. These symptom-symptom relations are not only likely to produce a considerable part of the empirical covariance between symptoms, but may also play an important generative role in the etiology of a disorder. To again contrast this situation with medical diseases, it is useful to note that the relation between symptoms and disease is typically causally asymmetric: the tumor causes foggy eyesight, not the other way around. However, in psychopathology, research suggests that mental disorders may be caused by the direct activation of symptoms through, for instance, adverse life events (Cramer et al. 2012, Keller et al. 2007). For example, the death of a spouse might trigger insomnia, which a few weeks later culminates into a full-blown episode of MD, and the mechanism that realizes this process is likely to involve symptom-symptom causation. For instance, one may consider a chain such as chronic stress → depressed mood → self-reproach → insomnia → fatigue → concentration problems. Such a chain results in five present symptoms and thus a diagnosis of an episode of MD. However, for a person who develops MD following major health problems, such as myocardial infarction, the route to MD may follow a different path and, for instance, start with somatic symptoms (De Jonge et al. 2006). Similarly, one may consider causal pathways such as having a panic attack → worry about the consequences of having such an attack (PD), and pathological use of cocaine → failure to be a responsible parent [substance use disorder (SUD)].

In sum, not only do we not know that symptoms are caused by mental disorders, but it is in fact extremely unlikely that they are. As a result, the hypothesis that such disorders are the proper entities to steer the organization of research, diagnosis, and treatment is, at best, awaiting scientific justification. Importantly, however, the different causal status of medical diseases and mental disorders with respect to their relations to symptoms does not merely infuse criticism of current approaches; it also suggests an alternative methodology that holds significant promise for the study of psychopathology. The heart of this approach lies precisely in what separates medical conditions from mental disorders: the general idea that causal, meaningful relations between symptoms not only exist and should be acknowledged, but in fact are the very stuff of which mental disorders are made.

COMPLEX PSYCHOPATHOLOGY NETWORKS

The foundation of the network approach is simple (Cramer et al. 2010, Schmittmann et al. 2013): Instead of interpreting symptoms as a function of a set of underlying/latent disorders, the network approach conceptualizes symptoms as mutually interacting, often reciprocally reinforcing, elements of a complex network. Thus, rather than interpreting symptoms as measurements of a latent disorder (as is depicted in **Figure 1**; see **Table 1** for the accompanying legend), symptoms are viewed as part of a causal system (Borsboom 2008a). As such, the relation between symptoms and disorder becomes one of mereology (a part–whole relation) rather than measurement (a causal relation; Reise & Waller 2009). In that respect, psychopathology symptoms are not symptoms in the strict sense of the word. Instead of passive receptors of the causal influence of a medical condition, symptoms are causally active ingredients of the mental disorders themselves.

It should be noted that this move from latent disorders to networks of causally connected symptoms is in itself a quite simple and straightforward matter. In particular, it does not involve the acceptance of any particular theory about psychopathology. It merely results from accepting two simple propositions: (*a*) Given the current evidence, we should forestall the conclusion that symptoms of the same disorder are uniformly caused by a single psychological or biological condition (or a single constellation of such pathological conditions), and (*b*) psychopathology symptoms

causally influence one another. Hypothesis *a* is merely a matter of scientific prudence, given the absence of credible mono-causal explanations for how psychopathology symptoms arise. Hypothesis *b* cannot reasonably be denied by anyone familiar with the symptoms that are typically listed in diagnostic systems in psychology.

Despite the fact that few scholars will be vehemently opposed to these hypotheses, the consequences of accepting them are potentially radical. First and foremost, if it is indeed the case that direct and possibly reciprocal interactions exist between symptoms, then it becomes unclear whether the disorder itself is at all required as a separate entity to make sense of the empirical correlational structure of symptoms. We do not need the disorder MD to explain why the symptoms of MD hang together: These symptoms are strongly correlated because they are part of the same system, i.e., because they causally influence one another. For example, decreased appetite and losing weight do not correlate highly because they are caused by the same disorder, MD, but rather because they are causally related: decreased appetite → losing weight. Second, if one accepts that symptoms and causal connections between them are what constitutes a mental disorder, then the term "comorbidity" gathers a different meaning: No longer can comorbidity be meaningfully explained as a correlation between two disorders, nor as the result of a common underlying (neurobiological) dysfunction or "super disorder" (e.g., Barlow et al. 2004). Instead, the causal relations between symptoms constitute pathways that can connect different disorders, for example via bridge symptoms (i.e., symptoms that are part of both disorders): chronic worry [generalized anxiety disorder (GAD)] → sleep problems (GAD/MD) → fatigue (GAD/MD) → depressed mood (MD).

As Cramer and associates (2010) have argued, such multiple pathways from one disorder to another might exist in such a way that there is no objective or "true" point at which to carve the symptom network in two, with each part representing a separate disorder. That is, as has been noted in the past (Kendell 1975, Klein 1978, Spitzer 1973, Spitzer & Endicott 1978), boundaries between disorders are fuzzy. Importantly, in the network approach these boundaries are fuzzy not as a result of methodological limitations, but rather as a result of the intrinsic structure of disorders. Thus, from this point of view, the current lack of separability of disorders is not a matter of resolution that will be resolved by the advent of future measurement techniques. Instead, the reason that we have been unable to find true boundaries is simply that there are no true boundaries. Although, in the network approach, one may still define disorders as sets of more densely connected symptoms that show synchronized behavior (like a school of fish or a flock of birds), these disorders are literally intertwined with one another and cannot be neatly separated. As a result, if one wants to cut nature at its joints in psychopathology research, one had better accept that the joints themselves are fuzzy.

A final consequence of accepting the premises of the network approach is that, with a shifting focus of scientific attention, the target of therapeutic interventions may change. Instead of some ephemeral "latent disorder," therapeutic interventions target symptoms and the relations between symptoms. This is a significant shift away from the emphasis of treatment in modern Western medicine, which generally aims for the identification of a root cause. For instance, if one has a headache as a result of a tumor, one could suppress that symptom by taking aspirin. However, this will not make the tumor go away: The tumor causes the headache, not the other way around, so a causal intervention at the symptom level cannot transmit its effect to cure the tumor. The only way to treat the condition is to remove the root cause and get rid of the tumor.

In contrast, in psychopathology, the idea that one can literally treat MD is entirely hypothetical, since there is no evidence that the label MD refers to a root cause or essential property shared by those who are in fact depressed. That is, if MD does not exist as an entity that exists independently of its symptoms (like a tumor does), attempting to treat it analogous to the way medical conditions

are treated (cutting away the tumor) is like trying to saddle a unicorn. Instead, what one can direct treatment at are the problems that people actually have and that, as a whole, constitute MD (rather than being caused by it). In other words, in a network approach, interventions are optimally targeted at the symptoms themselves or at the causal relations that connect them. In our opinion, this point of view sits well with many, if not all, therapeutic interventions currently in use (e.g., cognitive behavioral therapy).

CONSTRUCTING AND ANALYZING PSYCHOPATHOLOGY NETWORKS

In recent decades, the construction and analysis of complex networks, which have their roots in physics and mathematics (Erdös & Rényi 1959, Ising 1925), has become a thriving enterprise in many fields that deal with complex organizations of mutually interacting entities. The problem of finding a way to analyze such systems has culminated in a set of powerful empirical research methods, generically known as network analysis, that can be applied to many different domains (Barábasi 2011). One of the first papers to generalize the idea of marrying mathematical descriptions of network structures to diverse sets of data-driven networks was the classic by Watts & Strogatz (1998), which led to an avalanche of empirical and mathematical research on the structure and dynamics of complex networks. A good introductory text on the resulting literature is Newman (2010), while Kolaczyk (2009) and Barrat and associates (2008) yield excellent treatments of the applications of network modeling in dynamic models. Grimmett (2010) provides a technical introduction to more complicated probabilistic models, while Boccaletti and associates (2006) give a reasonably comprehensive and readable treatment of network approaches in different fields.

At its core, a network is simply a set of elements (nodes) that are connected through a set of relations (edges; see sidebar Practical Guide I: How to Build Networks). Elements as well as relations between elements can be virtually anything: For example, nodes in a network can be airports, with the relations being defined as the number of flights between these airports, or neurons with the relations being the number of times any two neurons fire simultaneously, or symptoms of MD and GAD that are connected when they belong to the same disorder (see **Figure 2*a*** for a network visualization of this structure and **Table 1** for the accompanying legend). Thus, the construction and analysis of networks are highly accessible in the sense that the application

PRACTICAL GUIDE I: HOW TO BUILD NETWORKS

Networks consist of two building blocks: nodes and edges. Nodes are usually visualized as circles and can represent any conceivable variable (e.g., symptoms, persons, airports, neurons). Edges are lines that connect these nodes, and they can represent any conceivable sort of relationship [e.g., (partial) correlations, odds ratios, neuronal connectivity]. To build a network, one first identifies the elements that will function as nodes. As an example, we use MD and GAD symptoms (see **Figure 2** and **Table 1** for the accompanying legend). Second, one determines what kind of relationship is represented by the edges. In **Figure 2*a***, we define the relation as being a symptom of the same disorder in DSM-IV: Any two symptoms that satisfy this relation are connected. These relations are coded in an adjacency matrix (see **Table 2**) with all symptoms as rows (i) and columns (j). In this example, this matrix contains a 1 at position i,j if symptoms i and j are connected, and a 0 otherwise (see also **Figure 2**). This matrix is subsequently used as input for visualizing the network. An alternative is shown in **Figure 2*b*** where the edges represent empirical correlations. In that case, the adjacency matrix equals the empirical correlation matrix.

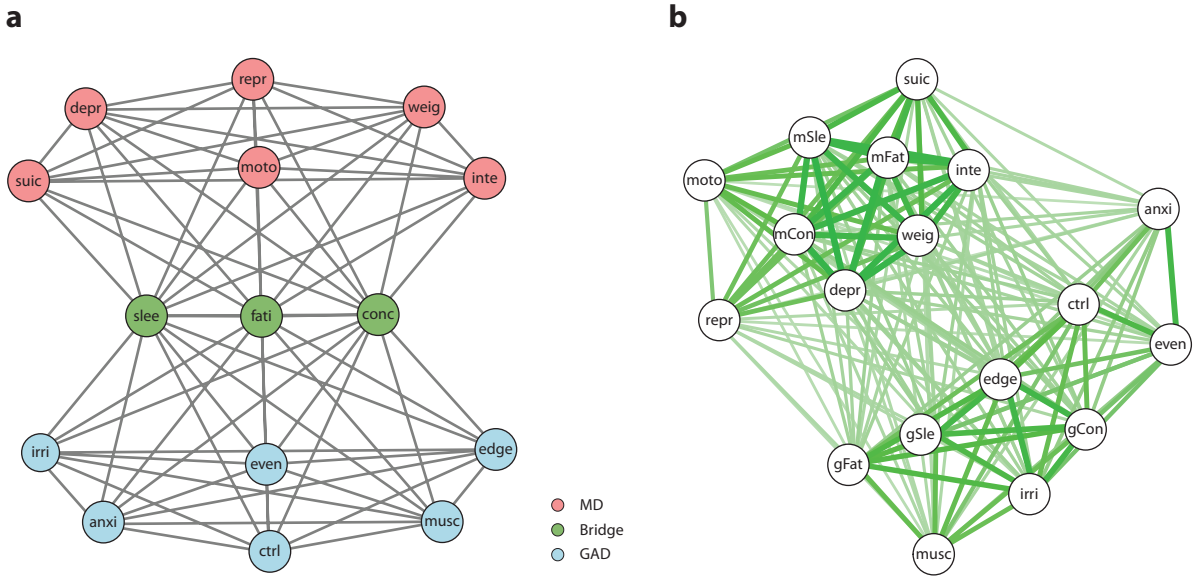

Figure 2

Networks for symptoms of major depression (MD) and generalized anxiety disorder (GAD) based on (*a*) the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) and (*b*) correlations based on the National Comorbidity Survey Replication data. (*a*) The symptoms of MD are placed at the top of the graph, bridge symptoms (i.e., symptoms that feature in both disorders) are in the middle, and GAD symptoms at the bottom. Symptoms are connected with a gray edge if they are part of the same disorder. Such a connection is coded in the adjacency matrix as a 1; no connection is coded as a 0. (*b*) The edges represent correlations. The higher the correlation, the thicker the edge. The position of the nodes in the network is based on an algorithm, which causes strongly correlated symptoms to cluster in the middle, whereas symptoms with weaker connections to other symptoms figure more in the periphery of the figure (**Fruchterman & Reingold 1991**).

Table 2 Adjacency matrix pertaining to Figure 2

	depr	inte	weig	moto	repr	suic	slee	conc	fati	anxi	even	ctrl	irri	musc	edge
depr	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
inte	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
weig	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
moto	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
repr	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
suic	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
slee	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
conc	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
fati	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
anxi	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1
even	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1
ctrl	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1
irri	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1
musc	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1
edge	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1

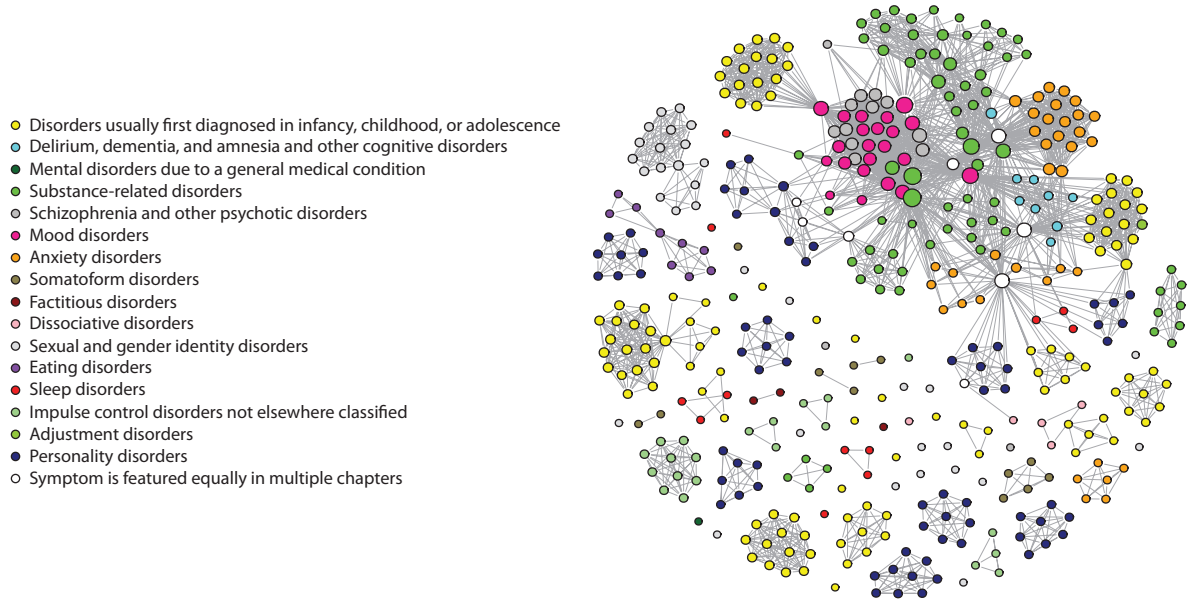

Figure 3

The DSM-IV symptom space. Symptoms are represented as nodes and connected by an edge whenever they figure in the same disorder. The color of nodes represents the DSM-IV chapter in which they occur most often. To view an interactive version of this figure, please download **Figure 3** from the **Supplemental Materials** page: **http://www.annualreviews.org/doi/suppl/10.1146/annurev-clinpsy-050212-185608**.

of network models does not require extensive prior knowledge, as many other methodologies do: All one needs is a set of elements and an idea of how these elements are connected.

Psychopathology networks can be constructed in several ways, each of which may yield important information about the structure of disorders. For instance, one can use the information in diagnostic systems themselves, as these often contain clues about the causal constitution of disorders. Second, one can use the assessment of (causal) relations between symptoms, as rated by clinicians or patients. Third, one may use data on symptom endorsement frequencies to extract empirical patterns of association that can serve as input for network structures; for example, as odds ratios, (partial) correlations, or pathways detected through causal search algorithms (Spirtes et al. 2000). Below, we illustrate how such networks can be constructed and analyzed with existing data.

Networks Based on Diagnostic Systems

Diagnostic systems like the DSM-IV or ICD-10 can be considered to partly reflect the structure of psychopathology through patterns of symptom overlap. A straightforward way of studying such patterns is by representing individual symptoms as nodes in a network and connecting them whenever they feature as symptoms of the same disorder (see sidebar Practical Guide I; see **Figure 2*a*** for an example of a DSM-based network structure for MD and GAD and **Table 1** for the legend). This type of network reveals the structure of the diagnostic system itself. For instance, Borsboom and associates (2011) used exactly the same procedure as in the sidebar Practical Guide I to analyze the full symptom space of the DSM-IV (Am. Psychiatr. Assoc. 1994). **Figure 3** shows the resulting network, which represents patterns of symptom overlap in the DSM-IV. One striking

PRACTICAL GUIDE II: COMPUTING PATH LENGTHS AND CLUSTERING OF BINARY NETWORKS

The shortest path length (SPL) between two nodes is the minimum number of edges that have to be traversed to reach one node from the other; for example, the SPL for anxi–fati in **Figure 2*a*** equals 1, whereas it is 2 for anxi–depr because they are not directly connected. The average shortest path length (ASPL) is the average of SPLs of all node-node pairs. In **Figure 2*a***, for instance, the ASPL is 1.253. Another measure of network size is the diameter of a network: the maximum path length between nodes in the graph. For the network in **Figure 2*a***, the diameter equals 2. The clustering coefficient C_i can be computed as follows. Suppose that a node i has k_i neighbors (the number of nodes with which node i is connected); then the maximum number of connections between these neighbors (MAX) equals $k_i(k_i–1)/2$: e.g., in **Figure 2*a***, irri has eight neighbors, so MAX $=$ 28, whereas slee has 14 neighbors, so MAX $=$ 91. C_i is the proportion of MAX that is actually present in the network. In **Figure 2*a***, C_i for irri is 1 (28/28) and 0.604 (55/91) for slee.

feature of this network is the emergence of a giant component—a large group of nodes that are all connected to one another, either directly or via intermediary nodes (Newman 2001a)—in which symptoms of mood (pink nodes), anxiety (orange nodes), and substance abuse disorders (green nodes) predominantly feature.

The giant component in **Figure 3** has the characteristics of what is known as a small world in the network analysis literature (Watts & Strogatz 1998); that is, on average, paths from one node to another are short and there is a large degree of clustering (i.e., the extent to which nodes tend to form a connected group; see sidebar Practical Guide II: Computing Path Lengths and Clustering of Binary Networks for how to compute shortest path lengths and clustering coefficients in the case of binary networks). Most people are familiar with this idea through the work of Milgram (1967), who was among the first to demonstrate empirically the small world phenomenon. Milgram (1967) famously instructed people to send letters to other people (i.e., targets) they did not know by giving the letters to acquaintances they felt might know the target (or to somebody who might know somebody who . . .). The people who received the letters then did the same. On average, it took six steps to reach the target, a result that became famous as "six degrees of separation." Thus, a small world structure implies that, even though a network may be very large and feature strong clustering, any node can be reached from any other node in only a few steps. For the DSM-IV network, the small world property means that comorbidity appears to be, at least partially and in particular for mood, anxiety, and substance abuse disorders, encoded in the structure of the diagnostic criteria themselves (Borsboom 2002).

Although the network in **Figure 3** directly represents the DSM-IV rather than the structure of mental disorders, it is not entirely unreasonable to suspect that the network may harbor relevant causal information. This is because the DSM itself frequently mentions (or even requires) causal relations between symptoms of the same disorders. For instance, for the diagnosis of PD, it is required that a person has panic attacks, worries about the implications of these attacks, and changed his or her behavior as a result of panic attacks. In this case, the latter symptoms clearly depend causally on the presence of panic attacks themselves, so much so that this dependence is required for the diagnosis (i.e., worry about something distinct from panic attacks does not count as a symptom of PD). Similar constructions arise for the diagnosis of SUD, in which it is required that the person experiences problems as a result of substance abuse; posttraumatic stress disorder, in which it is required that a person reexperiences traumatic events (in this case, the traumatic events are among the causes of reexperiencing them); and specific phobia, in which

all other symptoms (e.g., enduring the phobic situation with intense anxiety) causally depend on the first symptom of being excessively fearful of a particular object or situation. In addition, causal links that are not explicated in the system may occasionally be highly likely. For instance, in obsessive-compulsive disorder, compulsions are considered to be a means of reducing distress caused by obsessions (Franklin & Foa 2011; e.g., a person washes his or her hands compulsively to reduce the distress caused by the obsession with cleanliness). Thus, at least for a subset of psychopathology symptoms, it is possible that their causal connection is in fact the reason that they figure as symptoms of the same disorder.

As we view it, diagnostic systems like the DSM are thus not theoretically neutral, as has been claimed to be the case from DSM-III onward (Maser et al. 1991, Wakefield 1997). Rather, this diagnostic system is replete with clinically relevant causal relations like the ones outlined above. At the level of causal relations, therefore, the DSM does theorize and, at times, it does so to a great extent when it comes to the causal order of symptom development. It is important to note that psychometric analyses of systems like the DSM-IV with latent variable models that simply ignore such clinically relevant causal relations, which are explicated in the system itself, should be viewed with caution.

Perceived Causal Relations

A second way of gaining insight into the causal organization of disorders is by asking experts or patients to report causal relations between symptoms. To our knowledge, the first researchers to ask experts about perceived causal relations between symptoms were Kim & Ahn (2002). For disorders such as anorexia nervosa, antisocial personality disorder, and MD, they asked clinicians to draw a line between two symptoms whenever they thought these two symptoms were somehow related. The clinicians were specifically told that such relations could mean anything (non)causal, from "co-occurs with" to "causes." Whenever clinicians drew a line between symptoms, they were asked to indicate the strength of this perceived relationship on a three-point scale. We asked 12 Dutch clinicians to do the same for MD, GAD, and mania. The results pertaining to MD are shown in **Figure 4** (see **Table 1** for the accompanying legend), in which we have used an algorithm that positions strongly connected nodes in the middle of the graph and the more weakly connected nodes in the periphery of the graph (Fruchterman & Reingold 1991): for example, according to the Dutch clinicians the symptom "depressed mood" is important in the disorder because it has strong connections with most of the other symptoms in the network. In contrast, the symptom "weight problems" is perceived to be less important since the clinicians do not think it is strongly related to any of the other symptoms of MD.

Recently, Frewen and associates (2011) have developed a systematic approach to the investigation of causal relations between symptoms by means of questionnaires that may be administered to clients. They call this methodology perceived causal relations scaling. In this method, a person first indicates which of a set of symptoms is present. Secondly, each combination of presented symptoms (i,j) is combined in a question that assesses whether i caused j (reciprocal causal relations are typically allowed). In this way, one essentially builds a self-reported adjacency matrix for all symptom-symptom relations. That matrix defines a network that represents the cognitive representation of the causal structure of disorders. One could also see the network as a self-generated hypothesis on the network structure of a patient's disorder. The extent to which such hypotheses are in fact accurate is an important question for further research. If they are, then perceived causal relations scaling may offer a cheap and quick way to a rough assessment of psychopathology networks that could be used to construct informed treatment interventions.

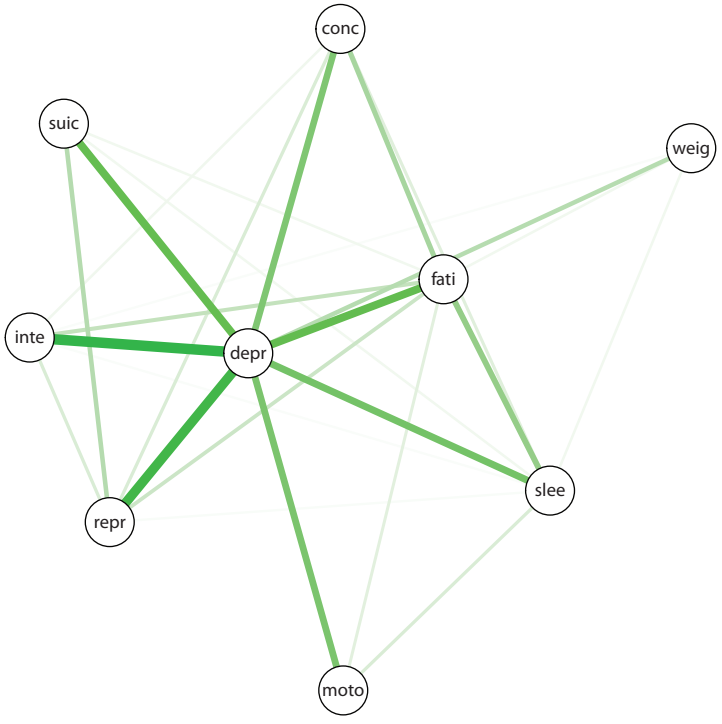

Figure 4

A network for MD based on the ratings of 12 Dutch clinicians. The nodes in the network represent the nine symptoms of MD; the edges between these nodes represent the mean connection strength between these symptoms as rated by the 12 Dutch clinicians (range: 0 = no connection; 3 = strong connection): The higher the mean rating, the thicker the edge. The position of the nodes in the network is based on an algorithm, which causes strongly correlated symptoms to cluster in the middle, whereas symptoms with weaker connections to other symptoms figure more in the periphery of the figure (Fruchterman & Reingold 1991).

Extended Psychopathology Networks

Networks for psychopathology feature relations between symptoms. Typically, we see these symptoms as interacting with one another at the level of the individual person. However, in some cases, one person's symptom may infect another person. Perhaps the most famous example of such a situation is the shared psychotic disorder or *folie à deux*. This disorder may involve the development of a delusion in one person, who then infects another through social communication. For instance, suppose that Bob becomes convinced that a government agency is spying on him. As a result of this symptom, Bob may keep the curtains closed, refuse to open the door, etc. Thus, Bob's primary symptom causes other symptoms, resulting in a network structure of psychopathology. Now imagine that Bob succeeds in convincing his spouse, Alice, of the veracity of his suspicions. As a result, Alice may also start withdrawing from social life and may develop symptoms similar to Bob's. Thus, the activation of Bob's symptom not only has produced other symptoms within his own system, but has also produced symptoms in another person. We propose to call such symptom networks extended psychopathology networks.

Extended psychopathology networks may be studied in more or less the same way as ordinary psychopathology networks, but are especially useful when time information is present, so that one can estimate person-specific networks (see section The Many Roads to Disorder: Individual

Networks) as well as the way they interact. Such methodology could be used to chart the interaction between symptoms of different people in various social situations. This would be relevant for childhood psychopathology, for instance, because it would allow one to study the interaction between parents and children as problems develop over time. To give one example, in the study of developmental psychopathology, reciprocal interactions may exist between sleep problems and behavioral problems (Patzold et al. 1998). Sleep problems of a child invariably lead to sleep problems of the parents; in turn, prolonged periods of poor sleep and behavioral problems in a child may lead to parental stress (Hoffman et al. 2008), which may result in less adequate handling of the child at bedtime, and hence leading back to sleep problems. Thus, in this case we have a feedback cycle that runs over symptoms that belong to various members of a family, and we see that the problems of neighboring individuals become intertwined.

Extending this idea further, one quickly reaches the conclusion that, in almost any mental disorder, significant social effects of this kind exist; in general, prolonged severe problems lead to a greater degree of social isolation. This means that the way in which one person's symptom network interacts with other people's networks leads to the alteration of that person's social network. Thus, carrying the idea of extended networks a little further, one sees a Russian doll of networks that are nested within other networks. Note that, even at this level, reciprocal influence is likely to be the norm rather than the exception, for the development of social isolation due to a network of personal problems may itself induce a further burden, thereby further enhancing the very problems that caused the isolated state in the first place. Thus, the complexity of psychopathology not only involves complex reciprocal relations between symptoms but also between networks of symptoms and social networks.

In this view, one follows the ladder upward, from symptom networks to social networks. Naturally, one can also extend networks in a downward fashion. For instance, one may unpack MD into a network of symptoms such as depressed mood and sleep problems. However, if one unpacks the concept of a sleep problem itself, one concludes that the symptoms themselves are complexly structured, with feedback cycles between hormones, external cues, and behaviors that give rise to the circadian rhythm. Thus, the reality of psychopathology involves a Russian doll of networks nested within networks in several layers of complexity. The exploration of such layered network structures is within reach given current data-gathering possibilities, and we think that the simultaneous analysis of social, symptom, and physiological networks is one of the main research challenges for the near future.

Association and Concentration Networks

Another way of exploring the causal organization of mental disorders is by studying empirical associations between symptom reports in patient or community samples. For instance, the matrix of correlations between symptoms is a symmetric symptom x symptom matrix, and as such, it can be treated as a weighted adjacency matrix (see sidebar Practical Guide I). **Figure 2*b*** shows such a network for symptoms of MD and GAD, in which the edges represent empirical correlations based on the NCS-R data (see **Table 1** for the accompanying legend). We interpreted missing values that arose from the skip structure of the questionnaire as absent symptoms and replaced these by zeros, which seems a reasonable course of action given the way the DSM-IV is set up. Naturally, other courses of action are possible, but these fall outside the scope of this review. What one immediately sees in this figure, for instance, is that MD and GAD are separated somewhat from each other in the graph; that is, the correlations within the MD network and within the GAD network appear to be stronger than correlations between MD symptoms on the one hand and GAD symptoms on the other hand.

Such association networks are very useful for seeing at first glance which clusters of symptoms tend to be strongly connected or not. However, if one is interested in knowing which of these symptoms are truly related (i.e., discovering the causal skeleton that gives rise to a particular correlational structure), then correlations may not provide optimal information. That is because a high correlation between any two symptoms might be the result of (*a*) a true direct (possibly reciprocal) relation between these two symptoms, or (*b*) a third variable that causes both symptoms, or (*c*) selection on a common effect of the symptoms (Pearl 2000). An example of the first possibility is a high correlation between decreased appetite and losing weight: Not only are we quite sure that a direct relation exists between these symptoms of MD, we can also be confident about the directionality of this relationship: decreased appetite → losing weight. This and other direct causal relations between symptoms (e.g., insomnia → fatigue; self-reproach → suicidal ideation) are likely to form the causal skeleton of MD. On the other hand, in the second case, for instance, we might find a high correlation between avoiding a phobic situation/object and feeling distress over having a specific phobia. Then it is possible (and perhaps likely) that these two symptoms are not directly related (neither avoidance → distress nor distress → avoidance) but that their association is caused by a third symptom of specific phobia: exposure to the phobic situation/object provokes intense fear, as a result of which a patient (*a*) avoids the phobic situation/object and (*b*) feels distressed about the whole situation (thus exposure → avoidance and exposure → distress). As such, in this example, a direct relation between avoidance and distress might not be part of the causal skeleton of specific phobia. Compare this situation with smoking: Having yellow-stained fingers and a nasty cough are—when sampled in a normal population—probably highly correlated but not because they are directly related. Their association instead arises because they are caused by the same phenomenon, namely, smoking.

How can one figure out which correlations are indicative of direct causal relations and which are not? In a first step, one may obtain the matrix of partial correlations—that is, the correlations between pairs of symptoms that remain when all other symptoms are controlled for—which may be considered to provide clues about the causal skeleton of a network (an undirected pattern of direct relations between variables). For example, one computes the correlation between X (e.g., yellow-stained fingers) and Y (e.g., having a nasty cough) given Z (e.g., smoking): If the resulting correlation approaches zero, then one has a good indication that X and Y are not directly related. **Figure 5** shows such a partial correlation network (only partial correlations >0.10 are depicted as edges in the figure) for the five symptoms of specific phobia, in which each correlation was computed when all other variables in the network were controlled for.

One sees, for example, that no substantial partial correlations remain between avoidance and distress, whereas a rather large correlation remains between exposure and avoidance. Such a partial correlation network is called a concentration graph (Cox & Wermuth 1993). Note that partial correlations computed between dichotomous variables are not statistically optimal and should be interpreted with some care; on the other hand, in our experience, more elaborate statistical methods tend to paint a qualitatively similar picture—just like Pearson correlations between dichotomous variables (point biserials) lead to roughly similar structures as more elaborate coefficients such as log odds ratios or tetrachoric correlations (see also Cramer et al. 2010). To the extent that this generalizes, network structures may be reasonably recovered from such approximations even though point estimates and standard errors for the relevant association coefficients may be inaccurate. Further methodological investigations are needed to determine to what extent this is true. Note that it is straightforward to lift this limitation by applying nonparametric conditional independence tests.

In the traditional disease model, the most interesting individual differences are to be found at the level of risk factors/dysfunctions that cause a particular disease, although, naturally, individual

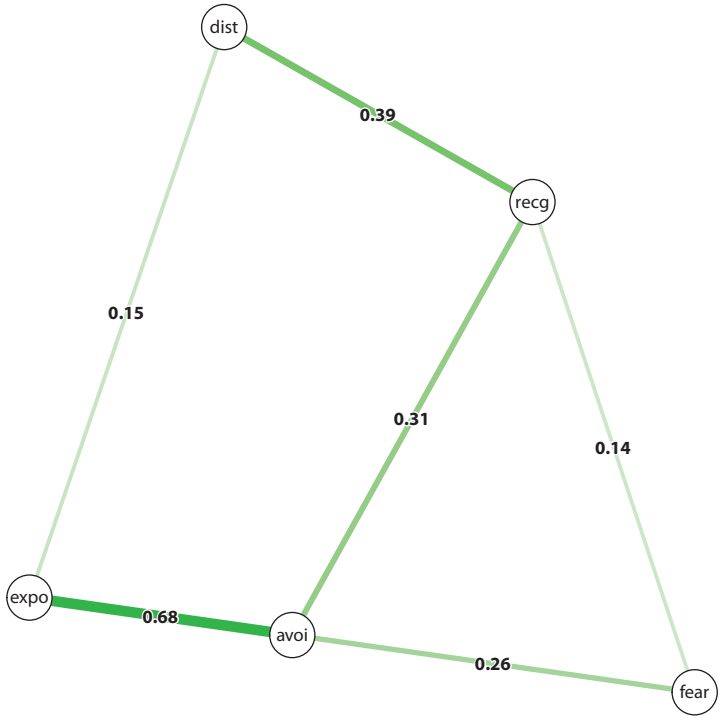

Figure 5

A network for specific phobia based on NCS-R data. The nodes in the network represent the symptoms of specific phobia; the edges between these nodes represent partial correlations >0.10: The thicker the edge, the higher the partial correlation. The value of each partial correlation is placed on top of its corresponding edge. The position of the nodes in the network is based on an algorithm that causes strongly correlated symptoms to cluster in the middle while symptoms with weaker connections to other symptoms figure more in the periphery of the figure (Fruchterman & Reingold 1991). Abbreviations: avoi, the phobic situation is avoided or endured with intense anxiety or distress; dist, marked distress about having the phobia or avoidance/anxious anticipation/distress in the feared situation interferes significantly with the person's life; expo, exposure to the feared situation almost invariably provokes anxiety, which may take the form of a situationally bound or predisposed panic attack; fear, marked and persistent fear that is excessive and unreasonable, cued by the presence or anticipation of a specific object or situation; recg, the person recognizes that this fear is excessive or unreasonable.

differences also exist at the level of the symptoms. That is, for instance, cancer research is dedicated to elucidate (*a*) which risk factors predispose someone for developing, say, lung cancer (e.g., smoking, working with asbestos) and (*b*) why when two people smoke, one does develop lung cancer and the other does not (e.g., a genetic mutation). Such research is not aimed at elucidating why one person with lung cancer does complain of chest pains while another patient with the same disease does not.

From a network perspective, these assumptions about individual differences change radically, because a network perspective predicts that relevant differences arise at the level of the symptoms and the relations between them rather than at the level of the disorder. Concentration graphs in particular are useful for an assessment of which pathways between symptoms appear to be common (see sidebar Practical Guide III: Computing Path Lengths and Clustering of Weighted Networks). That is, strong partial correlations in a between-subjects weighted network (like the one in **Figure 5**) may indicate that these pathways reflect real causal relations that are relatively

PRACTICAL GUIDE III: COMPUTING PATH LENGTHS AND CLUSTERING OF WEIGHTED NETWORKS

For computing SPLs, Dijkstra's algorithm minimizes the inverse of the distance between nodes i and j measured with weights w (Brandes 2001, Dijkstra 1959, Newman 2001b). In **Figure 5**, the shortest path from fear to recg is not the direct path ($1/0.14 = 7.142$) but rather the path via avoi: $1/0.26 + 1/0.31 = 7.071$. One can also include both the number and weights of edges in computing SPLs (Opsahl et al. 2010): A tuning parameter α is added such that $1/w_{ij}$ becomes $1/(w_{ij})^{\alpha}$. If $\alpha = 1$, only the edge weights are considered; if $\alpha = 0$, only the number of edges is considered. If $0 < \alpha < 1$, both the number and weights of edges are considered; e.g., when $\alpha = 0.20$, the shortest path from fear to recg is the direct path ($1/(0.14)\hat{}0.2 = 1.482$). The clustering coefficient $C^{w}{}_{i}$ is a generalization of C_i in the sidebar Practical Guide II (Barrat et al. 2004): $1/s_i(k_i-1)^{*}\Sigma_{j,h}(w_{ij} + w_{ih})/2^{*}a_{ij}a_{ih}a_{jh}$, with s_i = total weights of edges incident in node i, k_i = number of edges incident in node i, w_{ij} = weight of the edge between nodes i and j, and a_{ij} = binary operator indicating whether an edge exists between nodes i and j; e.g., in **Figure 5**, $C_3 = 1/0.85^{*}2^{*}\Sigma[(0.31 + 0.14/2) + (0.31 + 0.14/2)] = 0.264$.

common in the sample on which the network representation is based. For MD, for instance, one may find that a common trajectory runs via depressed mood, loss of interest, and fatigue (see **Figure 4** and **Table 1** for the accompanying legend). This formulation of common trajectories in terms of symptoms and relations between them deviates markedly from existing perspectives on pathways to disorder. Naturally, such identified pathways would need to be validated in another independent sample.

Directed Networks

Association and concentration graphs provide clues about possible causal relations between variables, but they do not provide information about the direction of causal relations (if these relations are unidirectional in the first place). The use of directed causal networks in statistical analysis has seen great developments in the past decades, especially in the work of Pearl (2000) and Spirtes et al. (2000). Unidirectional causal relations between nodes are typically represented by arrows. Causal analysis is easiest when the pattern of causal relations among variables creates a directed acyclic graph. In such a graph, all connections between nodes are directed, and it is not possible to visit any node more than once when traversing the edges along the direction of the arrows in the graph (this means that there are no feedback loops). Under a (strict) set of statistical assumptions, the causal network structure can be deduced from a set of observational data by exploiting the connection between causal relations and certain patterns of conditional independence (see sidebar Practical Guide IV: Conditional Independence Patterns for an elaboration on these patterns and **Figure 6** for a graphical example).

These relations have historically been used most often in structural equation modeling, where they serve to confirmatively test causal theories against the data. However, by cleverly using combinations of these relations, Spirtes et al. (2000) also developed inference algorithms that can be used exploratively. These algorithms effectively attempt to find candidate causal structures that could have generated the observed patterns of conditional independence relations. Danks et al. (2010) have suggested that such explorative approaches could be profitably used to build causal psychopathology networks. **Figure 7** (see **Table 1** for the accompanying legend) provides a graphical representation of the result of applying the PC algorithm (Spirtes & Glymour 1991) to the NCS-R depression data using the R-package PcAlg (Kalisch et al. 2012). The resulting

PRACTICAL GUIDE IV: CONDITIONAL INDEPENDENCE PATTERNS

The package PcAlg for R can be used to deduce the causal network structure from observational data. Three conditional independence patterns are particularly important in determining such a causal structure. First, a chain of three variables occurs when variable *Y* mediates the relation between two other variables *X* and *Z* (see panel *a* of **Figure 6**). In this case, *X* and *Z* are independent given *Y*. Second, a common cause structure or fork occurs when variable *X* is the common cause of *X* and *Z* (see panel *b* of **Figure 6**). In this case, *Y* and *Z* are independent given *X*. Third, a common effect structure or collider occurs when *X* and *Y* jointly cause *Z* (see panel *c* of **Figure 6**). In this case, *X* and *Y* will become conditionally dependent given *Z*, if they were unconditionally independent.

network accords well with the idea that the covariance between MD and GAD is mainly a result of the bridge symptoms they share (Cramer et al. 2010), as the PC algorithm does not detect any paths between MD and GAD symptoms that are not mediated through their common symptoms. Also, the MD network bears some resemblance to the clinicians' network in **Figure 4** (see **Table 1** for the accompanying legend). For example, in both networks, depressed mood only has outgoing arrows, suggesting that this symptom might come early on the road to developing MD by triggering the development of other symptoms (although some caution is in order here, since in the NCS-R data, people are interviewed about other MD symptoms only if either depressed mood or loss of interest is present).

THE MANY ROADS TO DISORDER: INDIVIDUAL NETWORKS

Between-subjects psychopathology networks are useful in, for instance, investigating the general structure of psychiatric disorders as they can generate testable hypotheses about trajectories toward developing a psychiatric disorder that are shared by individuals. However, such patterns of individual differences yield little insight when it comes to the question of how and why individual people develop disorders; for example, why Bob developed an episode of MD while Susan developed a phobic fear of spiders. In order to generate statements about the initiation, maintenance, and treatment of disorders of individuals, one needs to study the networks of individuals.

From a network perspective, each individual may have his or her own network, which comes with specific vulnerabilities or risk factors. **Figure 8** (see **Table 1** for the accompanying legend) shows two MD-GAD networks for two fictitious persons, Alice and Bob. The figure shows that Alice and Bob differ quite markedly in terms of how they can potentially develop MD and GAD.

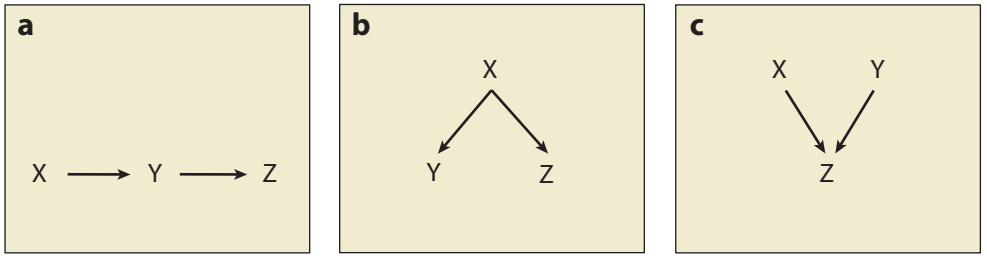

Figure 6

An illustration of the three most important causal relations that can be discovered through tracking conditional independence relations. Panel *a* shows a chain structure: *Y* functions as a mediator between *X* and *Z*. Panel *b* shows a common cause structure: *X* acts as the common cause of both *Y* and *Z*. Panel *c* shows a collider structure: *Z* is the common effect of both *X* and *Y*.

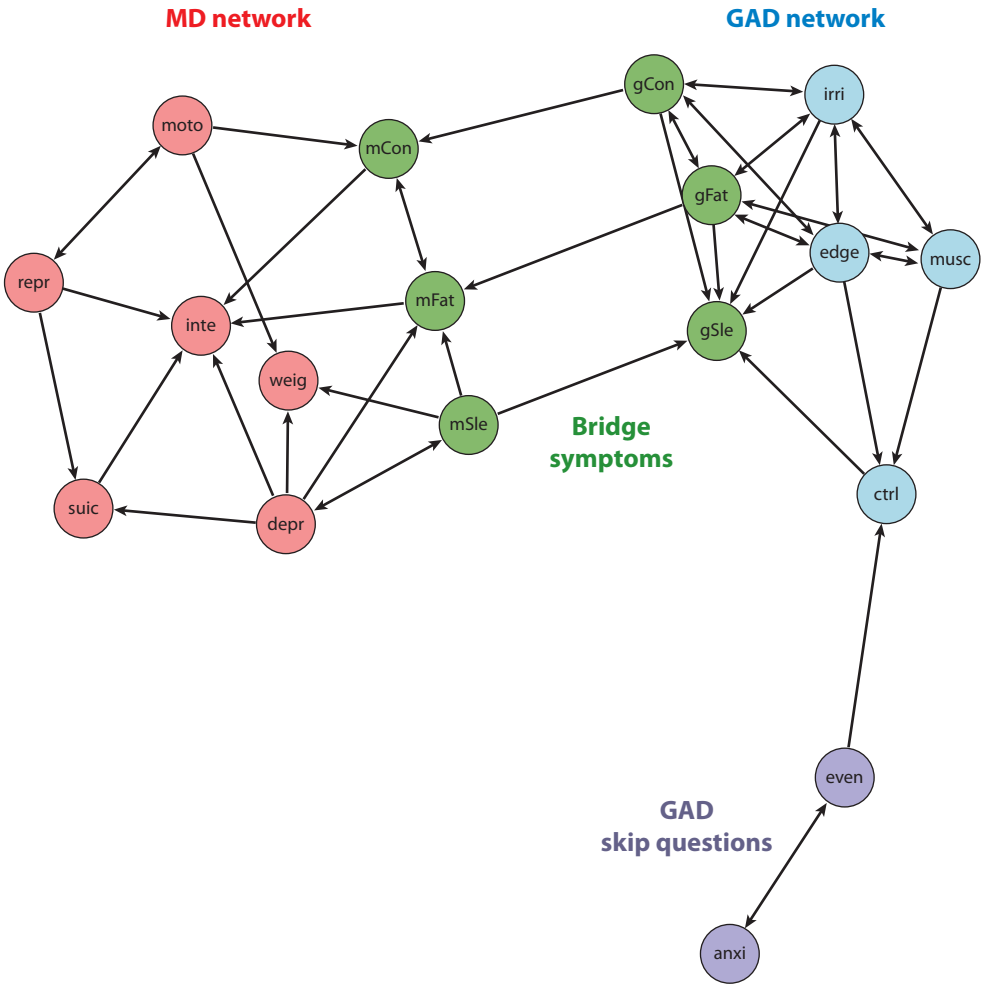

Figure 7

The directed MD-GAD network, based on the NCS-R data. Each edge represents a putative causal relation that remained after a search algorithm (PcAlg) tracked all the possible conditional independence relations present in the data. If two symptoms are not directly connected, this implies that they are independent conditional on a subset of other symptoms. Double-headed arrows represent connections for which the algorithm cannot settle on a direction.

For example, in Bob's case, the strongest pathway from MD to GAD runs via weig (weight problems), fati (fatigue), and edge (feeling on edge); in Alice's network, the progression of MD to GAD runs via depr (depressed mood), suic (thoughts of suicide), and irri (irritability). Since these are mere hypothetical examples of the many ways in which people can develop an episode of MD, what kind of data would we need to study these individual networks? And what can we infer from these networks in terms of individual risk of developing a certain disorder?

Time Series, Time Series, and Time Series

When the aim of network analysis is to construct disorder networks for individuals, cross-sectional data will be of little use. That is, in the networks of individuals, an arrow between any two

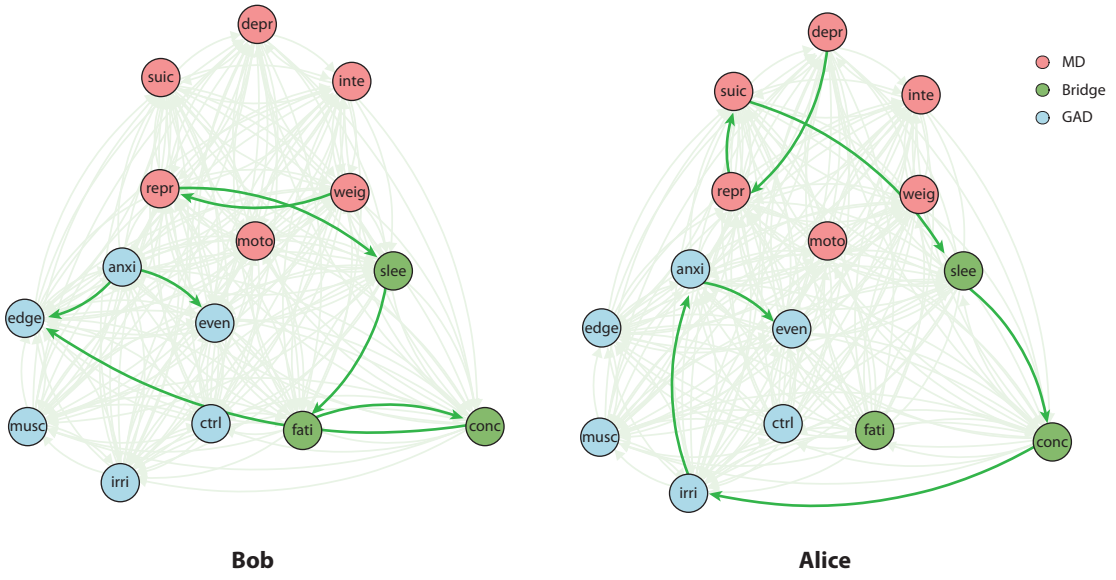

Figure 8

Hypothetical major depression (MD) networks for two fictitious people, Bob and Alice. Thicker green edges represent stronger causal relations between the symptoms of MD. These networks show that there are many ways to develop both MD and GAD

symptoms—say, insomnia → fatigue—is indicative of a process that takes place over time (e.g., insomnia develops at time t whereas the fatigue is caused by this insomnia at a later point in time, say, at time $t + 1$). As such, querying a person about his or her symptomatology at one point in time is simply not enough to extract the causal information necessary to build a network of this person's symptom space. As mentioned in the previous section, it is possible to ask people to draw their own causal scheme, but of course the success of such a method relies on the ability of people to accurately report on their symptom development retrospectively, which may not be equally accurate in all circumstances (Henry et al. 1994).

A viable alternative is to collect time-series data (Hamaker et al. 2005). That is, one asks individuals to report on various aspects of their physiological and psychological well-being at least once a day for many consecutive days. In one such recent research protocol, the experience sampling method (see Aan het Rot et al. 2012, Myin-Germeys et al. 2009), people are asked to report, during their normal daily life, their thoughts, feelings, and symptoms as well as the context in which these thoughts/feelings/symptoms take place and the appraisal of the context. One of the major advances of using such a method is that one is able to collect not only time-intensive data but also (*a*) data on the relation between events happening in a person's life and the subsequent ripple effects of that event in the symptomatology of this person, and (*b*) data from people without psychopathology who might be progressing toward developing a mental disorder. That is, in the latter case, one has excellent data to study why some people develop mental disorders while others do not, which in our opinion is the most pressing question in the entire realm of psychopathology.

Another possibility to learn about the intraindividual behavior displayed by a given network structure is by simulating time-intensive intraindividual data. With such simulated data, many of the interesting questions in psychopathology can be studied. For example, based on simulated data, Borsboom and associates (2011) showed that the percentage of "diagnoses" in simulated individual MD-GAD networks (in which comorbidity could only arise via bridge symptoms; see

PRACTICAL GUIDE V: SIMULATING NETWORKS IN NETLOGO

Our team developed a simulation model of MD that can be found at **http://ccl.northwestern.edu/netlogo/models/community/Symptom%20Spread%20Model** (van Borkulo et al. 2011). In this model, virtually anything—from symptom development to stressors—can be manipulated by the user. It works as follows. At each time point, the model computes the probability of each symptom *i* to become activated at the next time point with the logistic function $e^{\Sigma ax-b}/1 + e^{\Sigma ax-b}$. Here, Σax is the activation sum of all symptoms at the previous time point (coded in a vector x) times the weight of the relevant connections (collected in a vector a) and could be seen as the total incoming effect for symptom *i* at that time point; b is a vector of symptom-specific thresholds derived from the item difficulties of empirical data (Aggen et al. 2005). Two of the parameters that directly affect the probability functions in this basic setup and that can be altered by the user in real time are (*a*) number of connections (e.g., if all nine symptoms of MD are connected, then each symptom has eight neighbors) and (*b*) connection strength: The stronger the connections, the more influence the activation of symptoms has on other symptoms (thus directly affecting the *a* parameter vector in the model).

Figure 2*a* and **Table 1** for the accompanying legend) could account for prevalence rates for MD and GAD, comorbidity, and basic psychometric characteristics of the data at the same time. Also, based on a method to simulate data freely available online in the modeling environment NetLogo (Wilensky 1999), one can study the known impact of stressors (e.g., negative life events such as the loss of a loved one) on individual symptoms of MD and relations between them (Cramer et al. 2012, Keller et al. 2007; see sidebar Practical Guide V: Simulating Networks in NetLogo for the specifics of simulating data in NetLogo and **Figure 9** for a screenshot of the NetLogo simulation environment). Of course, through such exercises one primarily learns something about what behavior is actually implied by one's theory, but in the case of network models this way of working can be quite revealing.

The Analysis of Time Series

One can analyze time-intensive intraindividual data in a number of ways. The most straightforward way is to define connections in the network of an individual as representing the lag-1 correlations. That is, for example, if the network of Alice in **Figure 8** (see **Table 1** for the accompanying legend) would be a lag-1 correlation network based on empirical data, then the arrow from conc (concentration problems) to irri (irritability) means that concentration problems at time *t* predict irritability at time $t + 1$. Likewise, in Bob's network, the arrow from weig (weight issues) to repr (self-reproach) would mean that weight issues at time *t* predict self-reproach at time $t + 1$. If *t* would be measured in days, then a lag-1 correlation between feeling blue and eating more would probably be an appropriate time window; that is, it is plausible that feeling blue one day can make one eat more the next day. However, lag-1 correlations are probably not appropriate for other hypothesized relations between symptoms. For example, not sleeping for one night may not trigger fatigue immediately. Rather, one would expect a gradual build-up of sleepless nights, say, five, before true fatigue sets in. Thus, in this particular example, one would need to model this relationship in terms of a process that builds up over time.

Another option is to look at the entire available time window and define the connections between symptoms not in terms of (lag-1) correlations but rather in terms of the beta coefficients that result from a regression analysis through vector autoregressive modeling (Hamaker et al. 2007). For example, one could follow Bob for a prolonged period of time, assessing his depressive

Video

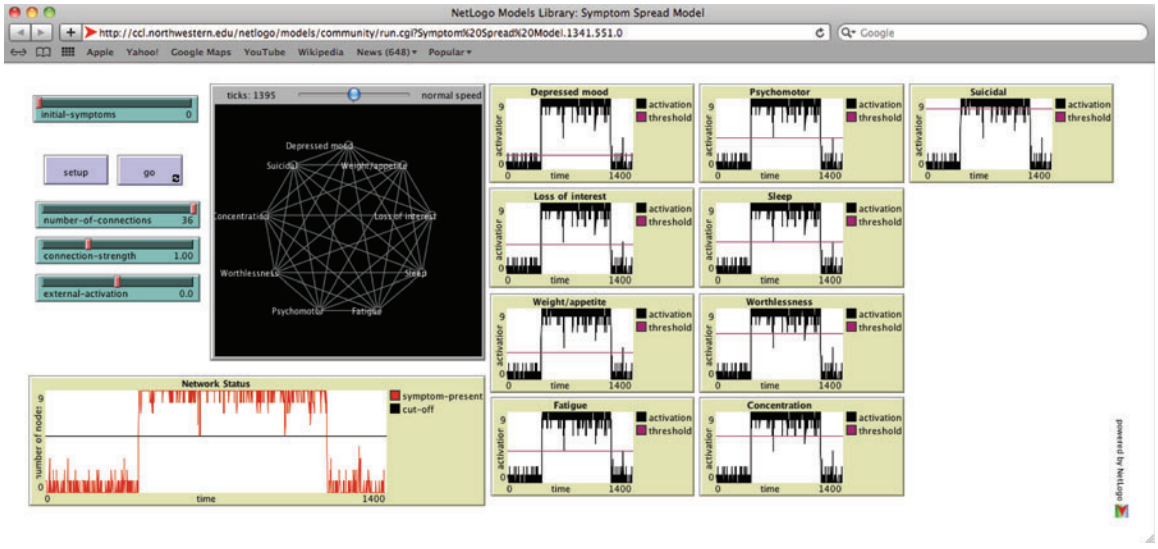

Figure 9

A screenshot of the Symptom Spread Model that can be used to simulate intraindividual dynamics for major depression. This model can be run online in the modeling environment NetLogo. To run the model directly in a browser, go to **http://ccl.northwestern.edu/netlogo/models/community/Symptom%20Spread%20Model**

symptomatology every day on seven-point scales. Then, one could compute partial correlations in order to get a rough idea of the causal skeleton of Bob's network. With this information, one subsequently determines the neighbors of each symptom: All connections that represent a partial correlation of 0.10 or less (or some other optimum at which all nodes are connected with a minimum number of edges) are deleted. In **Figure 5**, for example, this procedure resulted in fear having two neighbors; that is, fear is connected with two other nodes in the network, not with all four. Next, one regresses each symptom at time t on its neighbors on $t - 1$ and calculates the regression weights. These weights would then represent the strength of the connections in Bob's network. In a next step, one could attempt to determine directed acyclic graph structures for this type of data (Eichler 2007, Wild et al. 2007).

Thus, the analysis of time series could be executed in ways roughly similar to the previously discussed between-subjects data, but in this case to determine the network structure of the individual person. In general, a significant variety of models previously developed in econometrics and biometrics is available to construct network models (Kolaczyk 2009). This may offer genuinely new ways of charting intraindividual network structures. Further developing methodology to do this in psychological applications would greatly facilitate research in this area. In addition, intraindividual network structure could offer novel ways of planning treatment, for instance by targeting the most important symptoms in a person's network structure.

Risk in Individual Networks

Regardless of how one defines the connections in the networks of individuals, what can we say about risk in terms of these networks? As mentioned previously, in disease, risk is defined at the

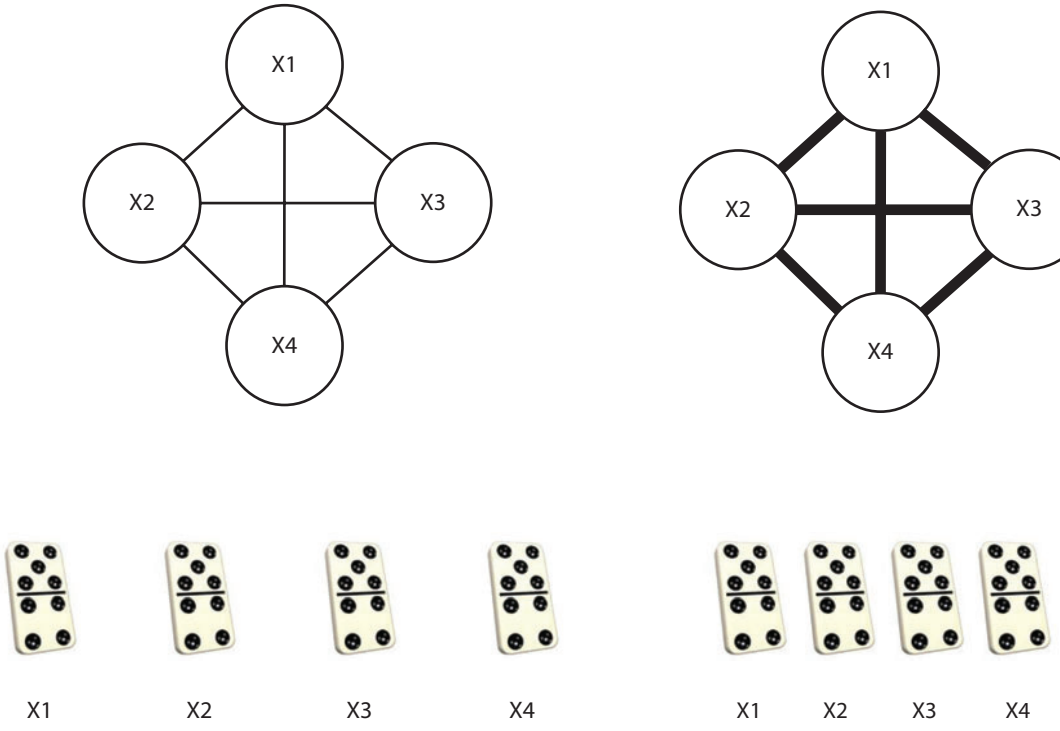

Figure 10

Two hypothetical networks of symptoms *X1–X4* (analogous to the domino tiles under the networks) that stand in certain relations toward one another (analogous to the distances between the domino tiles). In the left panel, the symptoms *X1–X4* are weakly connected, so in terms of the analogy, the distances between the domino tiles are relatively large. In the right panel, the symptoms *X1–X4* are strongly connected, so in terms of the analogy, the distances between the domino tiles are relatively short.

level of the disease entity, which is not present in a network, at least not as an entity that is separable from its symptoms. From a network perspective, there are at (at least) two ways in which a network can harbor risk of developing a certain mental disorder.

First, the structure of a particular network might be risky. To illustrate this concept, one may consider the symptoms of a disorder network to be domino tiles and view the connections between the symptoms as the distances between the domino tiles. Then relatively weak connections are analogous to domino tiles spaced rather widely apart (see left panel of **Figure 10**). As such, if, for instance, the symptom *X1* in **Figure 10** were to arise, then the probability of that symptom causing the development of other symptoms is relatively slim. In this case, the toppling of one domino tile will not likely result in the toppling of others, because they have relatively large distances between them. On the other hand, strong connections are analogous to domino tiles with short distances between them (see right panel of **Figure 10**). In that case, if symptom *X1* were to be developed, then its activation would likely spread through the network like a virus spreads through a population: The toppling of that one domino tile will likely topple the other dominoes as well because of the short distances between tiles. Thus, suppose that Alex has had a drinking problem in the past, which has caused all sorts of problems (e.g., financial problems, divorce from his wife), but at the moment he is sober after a successful intervention (see also Cramer et al. 2010). In that case, the structure of Alex's substance use network may still be risky, as there are only short distances between the domino tiles. Then, if Alex, for whatever reason, would have one drink, this

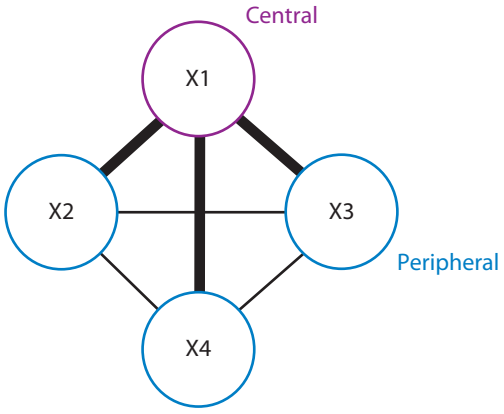

Figure 11

A hypothetical network of symptoms *X1–X4*. Symptom *X1* only has strong connections with the other symptoms in the network; this is a central symptom in this network. On the other hand, symptoms *X2–X4* all have one strong connection and two weak connections. These symptoms are thus peripheral in this network.

would quickly culminate in other symptoms, such as financial consequences and problems with the important people in Alex's life.

Second, there might be symptoms that, when developed in a particular person, have a stronger causal influence on the rest of the network compared to other symptoms. That is, in reality, different symptom pairs will have different connection strengths, which determine the extent to which symptoms causally influence one another (as opposed to the networks in **Figure 10**, in which all connections within one network were equally strong). Consider, for example, the network depicted in **Figure 11**. In this network, *X1* only has strong connections with the other symptoms in the networks; that is, *X1* is a central symptom in this network. On the other hand, the other symptoms, for example *X3*, have one strong connection but two weak connections; that is, *X3* is a peripheral symptom (as are *X2* and *X4*). Now, in terms of risk, the central nodes in someone's network are the most dangerous: If a central symptom is developed in someone, then the probability of that symptom causing the development of other symptoms is high (because the central symptoms are strongly connected to the other symptoms in the network); higher than when a peripheral symptom is developed (see sidebar Practical Guide VI: Centrality Measures for Weighted Networks).

Now, instead of defining risk or liability at the level of the disease, with largely untested or unconfirmed genes or other neurobiological pathological mechanisms as the culprit, the network perspective offers two concrete—and with good time-series data, testable—explanations of why certain people are at risk while others are not. Risk in terms of a network perspective is concrete in that it potentially gives therapists specific targets of where to intervene either to prevent the development of a full-blown disorder or to treat a person who already has developed a disorder. For example, the network perspective predicts that people who have developed a symptom that is central to, say, their MD network, are at risk of developing a full-blown episode. As such, targeting the central symptom with some kind of intervention, as soon as possible, should protect these people from progressing into disorder. Likewise, when treating patients who already have the disorder, it might benefit treatment if therapists knew where the strong and weak links are in the network; the strong links are pitfalls a patient could easily walk into (e.g., every time Susan feels somewhat blue, she starts thinking about ending her life), whereas the weak links are potentially easy to break.

PRACTICAL GUIDE VI: CENTRALITY MEASURES FOR WEIGHTED NETWORKS

One way to assess centrality is by computing the closeness (Opsahl et al. 2010) of node *i*, which is defined as the inverse of the total length of all SPLs between node *i* and all other nodes in the network. As explicated in the sidebar Practical Guide III, the shortest path calculation can take into account both number and weight of edges, depending on the tuning parameter α. For example, when one only considers the weights (i.e., $\alpha = 1$) in **Figure 5**, the closeness of avoi $=$

$$\left(\underbrace{1/0.68}_{\text{SPL[4,1]}} + \underbrace{1/0.26}_{\text{SPL[4,2]}} + \underbrace{1/0.31}_{\text{SPL[4,3]}} + \underbrace{1/0.31 + 1/0.40}_{\text{SPL[4,5]}}\right)^{-1} = 0.07$$

(e.g., SPL[4,2] = shortest path from node 4 to node 2).

A downside of closeness centrality is that one cannot compute it when one or more nodes are not connected (e.g., in **Figure 3**, nodes that are not part of the giant component) because then the SPL between two nodes becomes infinitely large. A measure without this problem is betweenness $(B_i) = g_{jk}(i)/g_{jk}$; g_{jk}: number of shortest paths between two nodes (if bidirectional then both path *i–j* and *j–i*); $g_{jk}(i)$: number of those paths that go through node *i*. For example, in **Figure 5**, the betweenness of fear is 0, and it is 8 for avoi.

CONCLUSION

The idea that mental disorders are network structures provides a new answer to the old question of whether mental disorders are real, and if so, in what sense. Quite a few scholars are essentialists in that they regard mental disorders as having some sort of essence, a key defining feature that separates one disorder from another or from mental health. In medical diseases, this often holds true; for example, the essence of Down's syndrome is a third copy of chromosome 21. But, as we have argued here, in the case of mental disorders, there is little evidence to suggest that essentialism is appropriate. In our view, it may very well be misguided. However, we do not resort to conventionalism to claim that mental disorders are constructed, like the concept of a yuppy is constructed out of the properties of being young, urban, and financially well off. There is definitely something real about mental disorders, but what? The network perspective gives that something a new face: causal networks of thoughts, feelings, behaviors, and physiological phenomena that, during someone's life, interact with one another and may, in some, rise to the level of mental disorder. To the extent that these causally active symptoms have been charted adequately, we thus already have a quite good idea of what constitutes mental disorders.

A development closely related to the network perspective is that of conceptualizing mental disorders as clusters of mechanistically connected properties (Kendler et al. 2011). This theory is analogous to the notion of homeostatic property cluster in biology, which gives a plausible account of how the concept of species may be real, but not in an essentialist way. In this theory, certain properties cluster because they produce a stable outcome. For example, that is why, in the animal world, the properties "weighing 4,000 kilos" and "having feet" cluster together (i.e., in an elephant, which represents a stable property cluster), whereas the properties "weighing 4,000 kilos" and "having wings" do not (i.e., a bird that heavy is not evolutionarily stable). Kendler et al. (2011) have argued that a similar account may offer a nonessentialist yet realist perspective on what constitutes mental disorders. In our view, this theory is quite plausible and rings well with the network perspective, in which causal clusters of symptoms correspond to mental disorders.

From both perspectives, it is a waste of time to search for the essence of MD or PD. The researcher who ignores the study of symptom dynamics to look for the essence of disorders could be likened to Ryle's (1949, p. 16) visitor to Cambridge who, after being shown the colleges, libraries, scientific departments, and administrative offices, asked "But where is the University? I have seen where the members of the Colleges live, where the Registrar works, where the scientists experiment, and the rest. But I have not yet seen the University. . .." However, this does not mean that research, originally aimed at uncovering essences of disorders (e.g., genomewide association studies, serotonin dysfunction research in MD), is unimportant and unnecessary. To the contrary, from a network perspective, such research endeavors are highly important. Rather, the key questions of such endeavors should be rephrased. Thus, instead of searching for "genes that cause MD" we are searching for "genes that cause certain risky network structures in individuals" (Cramer et al. 2011). Similar setups could be imagined for the study of group differences (would we find differences in the network structures of males and females for internalizing versus externalizing networks?), development (can we detect the formation of risky network structures in the developing child or adolescent?), and culture (do different cultural backgrounds foster different types of network structures?).

The study of network structures thus yields several new possibilities to go beyond the conventional classification of psychiatric disorders (Morris & Cuthbert 2012). This may be especially helpful for the study of the interaction of phenotype, neural development, environmental input, and behavior. Of particular interest is the analysis of endophenotypes (Cannon & Keller 2006, Gottesman & Gould 2003). In psychiatry, endophenotypes have been defined as (parts of) heritable phenotypes that are internal to the organism and that promote the development of psychiatric syndromes (Gottesman & Gould 2003). Typically, such endophenotypes have been taken to include cognitive dysfunctions and neural system dysfunctions, but also symptoms themselves (Cannon & Keller 2006). The network perspective adds the strength of interactions between symptoms as an important new possible endophenotype (e.g., individual differences in the strength of the link between insomnia and fatigue).

Following this line of reasoning, researchers might use time-series data to obtain a network model that describes the dynamic structure of individuals and use the parameters of that model, which differ over individuals, as endophenotypes. Such investigations are becoming realistic possibilities with the advent of experience sampling data-gathering techniques, models for interindividual differences in the intraindividual parameters of dynamics (Wang et al. 2012), and advanced statistical modeling techniques in behavior genetics (Boomsma et al. 2002, Franić et al. 2012). In an illustrative investigation along these lines, Wichers et al. (2007), for example, used experience sampling data to show that lifetime depression was positively associated with a bias to develop negative affect states in reaction to daily life stressors. A strong connection between symptomatic instances of negative affect (e.g., worry) and daily hassles may be viewed as a risky part of a person's network structure: It puts the person at greater risk for developing MD. It stands to reason that networks that contain more of these risky, negative connections and/or fewer positive ones (e.g., feeling happy and relaxed after the occurrence of a positive life event) have a riskier structure and elevate the chance that an individual will develop a disorder. Such an approach also resonates strongly with current conceptualizations in affective neuroscience, which view reciprocal causal links among cognitive, behavioral, and somatic mechanisms as crucial components in the genesis of affective disorders (Garland et al. 2010).

Networks may not only deliver a rich trove of alternative dependent variables that can be used in traditional experimental and quasi-experimental research setups, but may also alter our understanding of the relation between genes, brain, and behavior fundamentally. Traditionally, researchers tend to think of these levels as being intrinsically ordered, in the sense that genes

cause brains and brains cause behaviors. However, in our view it is extremely likely that once researchers start taking the dynamics of symptomatology seriously, they will find feedback loops that cross the borders of traditional thinking. Naturally, genetic differences may predispose to the development of disorders, but persistent symptomatology (e.g., insomnia or loss of appetite) may cause differential gene expression just as well; in turn, such changes may affect a person's brain state and ultimately feed back into the environment, as in the extended feedback loops discussed previously in this review (see also Borsboom et al. 2011). In our view, it is highly unlikely that one particular level of analysis will, in the end, be able to claim causal priority (see also Kendler 2012).

Finally, network analyses invite applications of techniques that are specific to complex network modeling. One such technique, which we think is especially apt to the study of psychopathology, comes from the study of sudden transitions in ecosystems (e.g., from tropical forest to savanna; Hirota et al. 2011). In dynamical systems, such transitions often occur when a parameter of the system crosses a so-called tipping point. It would be interesting to investigate whether tipping points can also be identified in network models for mental disorders. In addition, it is known that a wide variety of dynamical systems display characteristic behavior in the neighborhood of a tipping point (e.g., phenomena such as critical slowing down and increased variance; Scheffer et al. 2009), which possibly could be used to determine whether a person's network is on the brink of collapse.

As we have outlined in this review, a number of ways of charting the organization of mental disorders in terms of symptom interplay are already available. Several can be applied directly to existing data, as we have shown here. In our view, however, the most important progress in studying networks will be made with the analysis of data that represent the coevolution of symptoms over time. With current technology, there are few obstacles to gathering this type of data. Once such data become available, one can build person-specific networks, analyze their properties with the tools we outlined in this review, and then apply dynamical systems tools to chart and predict the course of such networks. Also, it becomes possible to target interventions at particular parts of a person-specific network (e.g., extinguish a central symptom such as insomnia) as well as monitor the impact of such person-specific interventions (e.g., how long does it take for the effect of treating insomnia to spill over to the other symptoms?).

Whichever theory of mental disorders one adheres to, they all share a deep desire to understand the inner workings of mental disorders. We all agree that finding out why some people are more vulnerable to developing mental disorders than others, how we can protect vulnerable people from harm, and how we can effectively treat people who have already fallen into the abyss of mental dysfunction are among the most pressing questions in the fields of clinical psychology and psychiatry. A disease model of mental disorders likely will not bring us any closer to finding answers to these questions. The network perspective very well might.

FUTURE ISSUES

1. How do people develop comorbid mental disorders? Answering this question calls for the construction of an empirical DSM graph in which symptom-symptom relations are constructed on the basis of empirical data, for example in the form of partial correlations or perceived causal relations.
2. What do the many roads to developing mental disorders look like? We need to collect time-intensive intraindividual data with which we can construct and analyze the networks of individual people. Can we then, for instance, observe that people with MD, for example, have a riskier network structure than people who do not have MD?

3. What sort of genetic/biological, psychological, and environmental factors govern individual differences in the strength of connections between symptoms? For example, what kind of processes are involved in a strong relation between feeling blue and contemplating suicide? And how do these processes differ from the ones that govern the relation between insomnia and fatigue? Answering these and related questions calls for the further development of methods suited to test causal relations between putative determinants of network structure (e.g., genes, endophenotypes, life events), symptoms, and symptom-symptom relations.
4. Are there tipping points in the networks of individuals for various mental disorders at which a person is at the brink of tipping into a disordered state or returning to mental health? Finding these tipping points might be important in directing the timing of therapeutic interventions.
5. How can the network approach help in targeting and evaluating therapeutic interventions? One may, for instance, investigate whether it is most effective to treat a central symptom in a client's network. Also, with the methods we outlined to collect time-intensive intraindividual data, it becomes possible to study how long it takes for an intervention to have an effect on symptoms and relations between them.

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Contents

Indexes

Errata

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