A Complex Network Perspective on Clinical Science

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Abstract

Contemporary classification systems for mental disorders assume that abnormal behaviors are expressions of latent disease entities. An alternative to the latent disease model is the *complex network* approach. Instead of assuming that symptoms arise from an underlying disease entity, the complex network approach holds that disorders exist as systems of interrelated elements of a network. This approach also provides a framework for the understanding of therapeutic change. Depending on the structure of the network, change can occur abruptly once the network reaches a critical threshold (the *tipping point*). Homogeneous and highly connected networks often recover more slowly from local perturbations when the network approaches the tipping point, potentially making it possible to predict treatment change, relapse, and recovery. In this article, we discuss the complex network approach as an alternative to the latent disease model and its implications for classification, therapy, relapse, and recovery.

Symptoms of mental disorders do not occur randomly; some are more likely to co-occur than others. The traditional psychiatric explanation for such co-occurrence is that symptoms reflect an underlying disease entity that causes their emergence (e.g., Guze, 1992). Just as a malignant lung tumor is the cause of co-occurring breathlessness, bloody sputum, coughing, and chest pain, so too is underlying depression deemed the common cause of insomnia, loss of appetite, impaired ability to feel pleasure (*anhedonia*), and unremitting sadness (cf. Borsboom & Cramer, 2013). Another explanation is that symptoms reflect underlying dimensions (e.g., neuroticism), not discrete, categorical entities (e.g., Krueger & Markon, 2014). The most recent edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–5*; American Psychiatric Association, 2013) retains an emphasis on categorical diagnoses despite their limitations (for a review, see McNally, 2011, pp. 184–211).

Psychopathologists have long debated whether disorders differ by kind (i.e., are qualitatively distinct categories) or degree (i.e., vary dimensionally). Debates between proponents of categorical and dimensional diagnoses have been contentious, yet both sides share an implicit understanding of the relation of symptom to disorder. Both assume that symptoms reflect the presence of an underlying, unobserved, latent construct, whether it is construed categorically or dimensionally (Bollen & Lennox, 1991; Brown & Barlow, 2005; Edwards & Bagozzi, 2000; Hofmann, 2014, 2015; Insel, 2014).

However, for an inference to a latent variable as the common cause of symptom covariance to be justifiable, there cannot be any causal connections among the symptoms themselves (i.e., the axiom of local independence must hold). That is, the covariance among symptoms must disappear if one makes them conditional on the presence of the disorder (Borsboom, 2008). This holds true for symptoms of lung cancer, for example, because controlling for the presence of a tumor eliminates the correlations among coughing, chest pain, breathlessness, and

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chest discomfort. It also holds for Down syndrome, where intellectual deficiency, a crease across the palm, short stature, and protruding tongue co-occur because they share a common cause: three copies of chromosome 21. No direct causal relations occur between a protruding tongue and short stature, for example. But the situation is different for depression and most other psychiatric syndromes where obvious causal connections among symptoms occur. For example, people who ruminate will likely experience insomnia, and sleep deprivation will cause fatigue the following day, thereby impairing their concentration, lowering their mood, and so forth (Borsboom & Cramer, 2013). Clearly, causal relations abide among such symptoms of depression—a conclusion forbidden by the psychometric requirements of both latent categorical and latent dimensional models of psychopathology (for reviews, see Borsboom & Cramer, 2013; Hofmann, 2014, 2015).

The *complex network* approach to conceptualizing psychopathology has emerged as a potentially game-changing alternative to both the latent categorical and the latent dimensional approaches (Borsboom & Cramer, 2013; Schmittmann et al., 2013). According to this view, symptoms do not reflect an underlying latent disease that causes their emergence and co-occurrence. Rather, symptoms constitute the disorder—they do reflect it. Hence, a disorder is not the underlying cause of symptoms; it constitutes a network of symptoms that interact in ways that tend to maintain themselves. Accordingly, a stressful event does not activate an underlying entity called *depression*, which then causes the emergence of symptoms. Rather, stressful events activate certain symptoms that, in turn, activate other symptoms, and when the requisite number of symptoms occurs, an episode of disorder may be diagnosable. The term *symptom* implies that sadness, anhedonia, loss of appetite, insomnia, and so forth reflect the presence of an underlying disease entity that causes their emergence. Accordingly, to avoid this implication, we follow Snaith (1993) and use the term *element* instead of *symptom* in this article.

Our purpose in this article is to discuss the complex network approach to clinical science. We first describe the essential elements of complex network analysis and then illustrate its implications for classification, treatment, and relapse. On the basis of this approach, disorders differ as a result of differences in the number, nature, and interrelatedness of their elements that constitute the network. This perspective offers exciting new opportunities not only for psychopathology and nosology (Borsboom & Cramer, 2013) but also for predicting treatment outcome, relapse, and recovery. We focus on network topology (i.e., structure) as applied to psychological problems and then shift to network dynamics (i.e., how networks evolve over time), especially in relation to the transition from health to illness and vice versa. But first we provide an overview of complex network analysis.

A Brief Introduction to Complex Networks

Network theory is a subset of graph theory, a branch of mathematics concerning the visual representation of a set of objects and the links connecting pairs of objects (Christakis & Fowler, 2009). Networks contain two components: *nodes*, which represent objects (e.g., individual persons, neurons, symptoms, and nations), and *edges*, which are lines that connect two objects, representing the association between them (e.g., a connection between two friends in a social network). In an unweighted network, an edge merely depicts whether two nodes are connected (e.g., a line between Tom and Julian indicates their friendship), whereas in a weighted network, the edge also represents the strength of association (e.g., an edge appears with a Pearson's *r* correlation coefficient indicating the magnitude of association between insomnia and fatigue computed over a number of individual persons).

Network theory enables computation of centrality metrics that reveal the importance of a node in the network. A highly central node is one that, when activated, is likely to spread activation throughout the network via the edges connecting it to other nodes. For example, a node high on *degree centrality* is one with many edges connected to it (e.g., a highly popular person in a social network). A node high on *strength centrality* in a weighted network has many edges with high magnitudes of association connected to it (i.e., the Pearson's *r* of each edge is large). A node high on *betweenness centrality* is one that often lies on the shortest pathway between two other nodes (e.g., a large department store that mediates the selling of items from many producers to many customers).

Complex networks comprise many nodes whose connections are neither random nor uniform (Barabási & Albert, 1999; Watts & Strogatz, 1998). That is, the structure (i.e., *topology*) of the network varies; some nodes cluster in subgroups, whereas others have few or weak connections with other nodes. Complex networks are the empirical norm in sociology, neuroscience, and psychopathology, as we describe in more detail below. Repeated assessments of the nodes and edges of a network reveal how networks evolve over time (e.g., network dynamics), evinced by the trajectory or recovery from a mental disorder.

The Complex Network Perspective on Psychopathology

Although still in a nascent stage, complex network approaches have attracted the attention of researchers from many different fields.[1] Following suit, clinical researchers are increasingly applying network analysis to elucidate depression (Bringmann, Lemmens, Huibers,
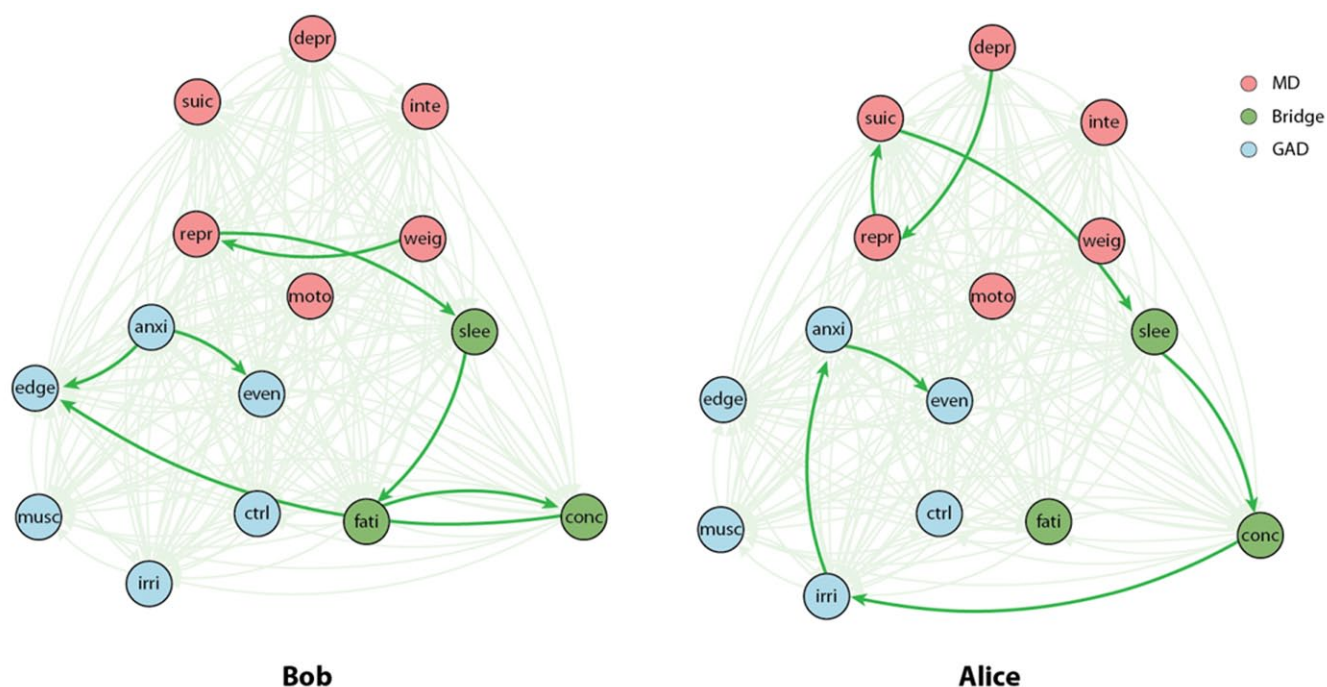
Fig. 1. Hypothetical examples of individual complex networks for two people, Bob and Alice. The red circles show the nodes of the network that are part of the major depression (MD) network (suic = suicidality; inte = loss of interest; depr = depressed mood; repr = self-reproach; moto = psychomotor disturbances; weig = weight problems); the blue circles are the nodes that are part of the generalized anxiety disorder (GAD) network (anxi = chronic anxiety and worry; edge = feeling on edge; even = anxiety about more than one event; ctrl = no control over anxiety; musc = muscle tension; irri = irritability); and the green circles are part of both networks, bridging them (slee = sleep problems; fati = fatigue; conc = concentration problems). The arrows depict hypothetical causal links and the thickness depicts the hypothetical strength of the causal relations. From "Network Analysis: An Integrative Approach to the Structure of Psychopathology," by D. Borsboom & A. O. J. Cramer, 2013, *Annual Review of Clinical Psychology, 9*, p. 110. Copyright 2013 by Annual Reviews. Reprinted with permission.

Borsboom, & Tuerlinckx, 2015; Cramer, Borsboom, Aggen, & Kendler, 2012; Fried, Epskamp, Nesse, Tuerlinckx, & Borsboom, 2016; van de Leemput et al., 2014), complicated grief (Robinaugh, LeBlanc, Vuletich, & McNally, 2014), generalized anxiety disorder (Fisher, 2015), and posttraumatic stress disorder (McNally, 2012; McNally et al., 2015). These studies provide an initial glimpse of the complex network structure abiding among elements of these syndromes. Using large numbers of subjects, researchers have computed networks illustrating how elements of these syndromes are associated, thereby providing visual depictions of potentially causal relations among them.

An example of how the complex network approach can be applied to specific cases is presented in Figure 1. This figure depicts hypothetical examples of individual networks for two people, Bob and Alice (Borsboom & Cramer, 2013). These two individual networks illustrate that there are many ways that major depression and generalized anxiety disorder can be connected through common nodes. Most relevant for deriving treatments are individual networks.

An intervention that effectively targets one element often influences many other elements that are connected in the same network. Elements connected into networks can settle into distinct, stable states (e.g., healthy vs. pathological). Although there will be as many networks as there are individuals (because it is unlikely that any two individuals will share the identical network), some features of these individual networks are likely to be more common across these networks than others, which will allow for the categorization of individual networks on the basis of similarities in the structure and elements.

Implications for Diagnostic Classification

What, then, are the diagnostic implications of the network perspective? First, it offers a new way of understanding disorders rather than a new way of diagnosing them. That is, the network perspective provides a new ontology for mental disorders (McNally, 2012), not an alternative to the *DSM* or the *International Classification of Diseases*. It directs attention to the defining features of

the pathology (nodes) and their functional interconnections (edges) and away from a search for an underlying common cause of the activated elements, expressed as a sum score designed to index severity (e.g., Fried & Nesse, 2015). It recommends a search for mechanisms (or *biomarkers*) causing specific elements (e.g., anhedonia) instead of disorders (e.g., major depression).

Second, the network perspective acknowledges heterogeneity within diagnoses, but it conceptualizes it differently than the *DSM* has. Subtyping different patterns of symptoms within a diagnostic category has been the traditional approach to heterogeneity (e.g., melancholic depression, atypical depression). Rather than interpreting heterogeneity as reflecting distinct latent variables within a diagnostic category, each with its own common cause, the network perspective views heterogeneity as common patterns suggestive of causal links between features of a disorder (e.g., diurnal variation of mood and early morning awakening in the melancholic network).

Third, the network perspective offers a distinct approach to differential diagnosis. For example, consider someone who has experienced a car accident and now fears driving. The traditional approach implies that an assessor needs to determine whether fear and avoidance of driving is reflective of the underlying condition of a specific phobia or posttraumatic stress disorder (e.g., McNally & Saigh, 1993). Yet, the question should not be whether the driving fear is due to a specific phobia or posttraumatic stress disorder, as the *DSM* asks; rather, the assessor should investigate what other symptoms are active and how they relate to one another. This approach is reminiscent of the pre-*DSM–III* functional analysis favored by behavior therapists (e.g., Goldfried & Davison, 1976), except that the latter tended to emphasize links between environmental stimuli—antecedents and consequences—and symptoms more than functional relations between symptoms, but with some notable exceptions (e.g., functional relations between obsessions and compulsions).

Fourth, as Cramer, Waldorp, van der Maas, and Borsboom (2010) demonstrated, network analysis can better address the comorbidity problem. Traditional diagnostic efforts have endeavored to purify disorders of nonspecific symptoms that appear in multiple diagnoses (e.g., sleep disturbance, concentration impairment; Spitzer, First, & Wakefield, 2007), thereby sharpening the distinction between disorders that are often comorbid. Rather than removing these nonspecific elements, the network analytic framework emphasizes them. Indeed, it views them as extremely important bridges, which, if activated, will transmit activation to features of several related disorders. Therefore, the network approach does not provide a replacement for the *DSM*. Rather, it provides a new way of understanding the relation between disorders and their defining features.

Implications for Therapy, Recovery, and Relapse

The complex network perspective has direct implications for understanding therapy, recovery, and relapse. Specifically, local or individual networks can provide valuable information for treatment planning and treatment targets. In fact, work on complex network models of aquatic systems by the ecologist Scheffer et al. (2009, 2012) are directly relevant for transitions from mental health to mental disorder and vice versa. This approach derives from chaos theory and catastrophe theory to explain nonlinear, dynamic, and transitional phenomena (e.g., Scheffer et al., 2009; Thom, 1977; Vandervert, 1991).

An important feature of a dynamic system is that it is characterized by *attractor* states, in which a given network achieves equilibrium and increased stability. When a network is in such a stable state, disturbances tend to disrupt the equilibrium only temporarily, as the network tends to return quickly to the attractor state once the disturbance passes. However, some disturbances may push the network over a critical threshold, tipping it into a new, stable state. This can happen when a major stressor destabilizes a healthy network, tipping the person into a depression network.

The key characteristics to understanding network changes from one state to another lie in the connectivity of the nodes of the network and its homogeneity. *Network connectivity* refers to the degree to which the nodes are connected with each other. A network has a high level of homogeneity if the nodes show a high level of similarity. For example, in the case of depression, the nodes low self-esteem and suicidal ideation are more similar than are the nodes low self-esteem and diminished appetite (because self-esteem and suicidal ideation are both cognitive elements, whereas diminished appetite is neurovegetative). Networks that are homogenous and highly connected tend to show bistability (i.e., they are either pathological or nonpathological).

Resilience denotes how quickly a system recovers from perturbations. Highly connected and homogeneous networks tend to be resilient to change; destabilizing events alter the configuration of nodes only temporarily. Strong local connectivity among a cluster of neighboring nodes promotes *local resilience* because the entire network can compensate for the destabilizing effects of local perturbations. The ability of the network to compensate for local perturbations is linked to the structure of the network. Networks with highly connected nodes are more stable, as depicted by the deeper valley in Figure 2. A complex system that occupies a pathological state is resilient if attempts to change it fail (i.e., the attractor state is strong), thereby preventing the system from reaching the *tipping point* to move from one state to
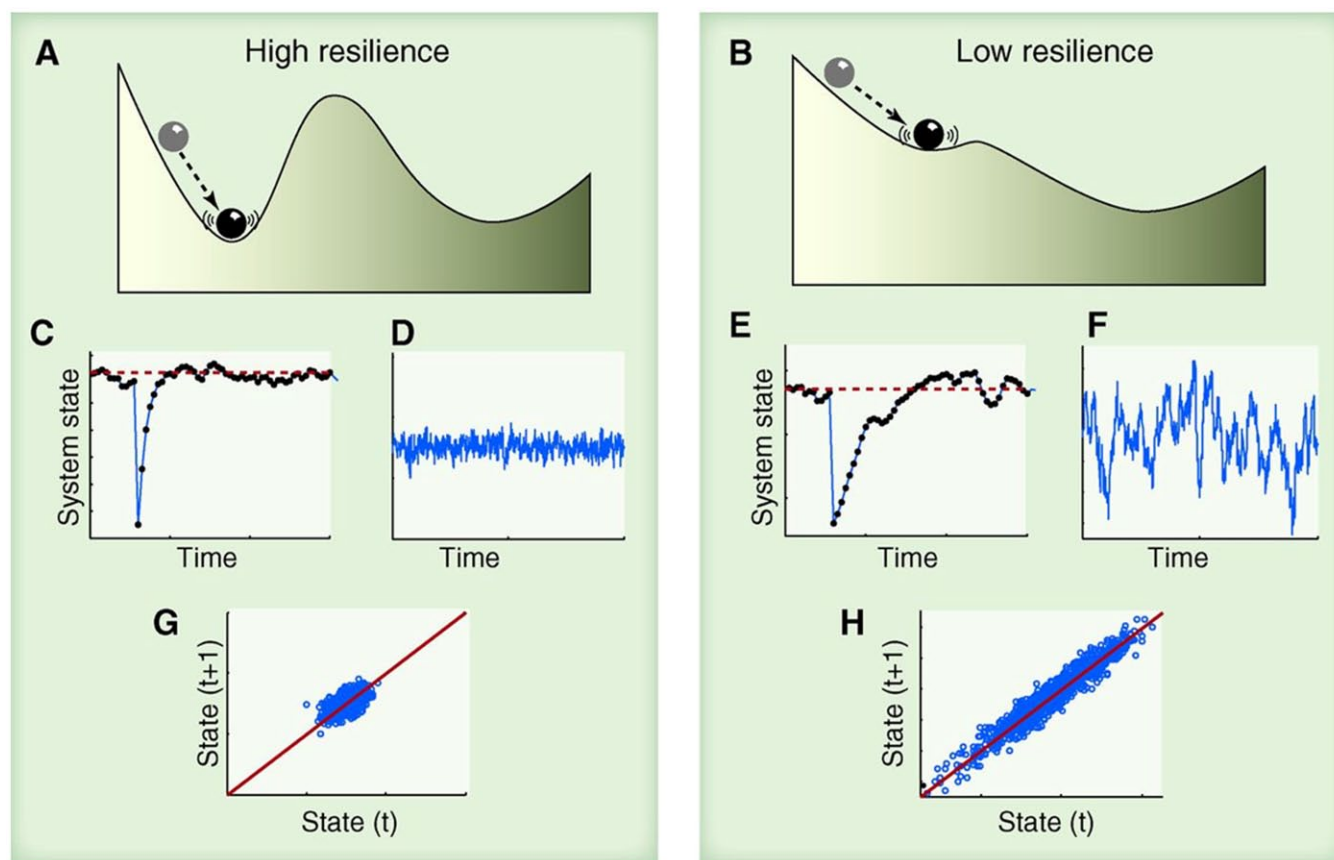
Fig. 2. Critical slowing down as an indicator that the system has lost resilience and may therefore be tipped more easily into an alternative state (for explanation, see text). From "Anticipating Critical Transitions," by M. Scheffer, S. R. Carpenter, T. M. Lenton, J. Bascompte, W. Brock, V. Dakos, . . . M. Pascual, October 19, 2012, *Science, 338*, p. 345. Copyright 2012 by the American Association for the Advancement of Science. Reprinted with permission.

another. Weak connectivity typically causes the network to change gradually in response to external influences, because weakly connected and isolated nodes tend to shift independently of one another. In contrast, in the case of homogenous and highly connected systems, a local perturbation can cause a domino effect cascading into an abrupt and systemic transition to another attractor state when a tipping point is reached (e.g., Scheffer et al., 2012).

From a complex network perspective, effective therapy, whether behavioral or pharmacological, attempts to destabilize the pathological state, moving the network over the tipping point to reach a nonpathological state. In the case of relapse, the system moves from the non-pathological to the pathological state. Scheffer (2010) has identified certain features of dynamic systems that signify when a dynamic system is approaching a tipping point, potentially suggesting that therapists may be able to identify signals of impending relapse.

Scheffer et al. (2012) depicted this phenomenon with a comparison to a ball rolling across a valley and hill (see Fig. 2). A network is more resilient and stable if the valley is deep; it requires more effort to move the ball out of the valley and over the hill. In contrast, the network is less resilient if the valley is shallow, as less effort is required to move the ball out of the valley. As a result, recovery rates after small perturbations (see Figs. 2C and 2E) are slower if the basin of attraction is small (see Fig. 2B) than if the attraction basin is large (see Fig. 2A). Under conditions far from the tipping point, a network is resilient because the basin of attraction is large, and perturbations will not easily drive the network toward an alternative stable state.

Networks comprising highly interconnected nodes can reach a tipping point where a local perturbation causes a domino effect that cascades into a systemic transition if outside disturbances satisfy a critical threshold. In mental health, these disturbances may be adverse life events or other stressors. In contrast, networks that are not highly interconnected (i.e., networks characterized by weakly or incompletely connected nodes) are more likely to change gradually in response to such perturbations. Complex

systems can give the false impression of resilience after repeated recovery from small-scale perturbations when, in fact, the network is moving toward a tipping point (e.g., from nondepressed to depressed), leading to a systemic shift (which network theorists call a *catastrophic bifurcation*). Requisite for such a sudden transition is a positive feedback loop that propels the network toward an alternative state once a critical point is passed. For example, one cognitive model of panic holds that panic attacks result from a feedback loop whereby certain bodily sensations (e.g., a skipped heartbeat) provoke a catastrophic appraisal of the sensation (e.g., "I'm having a heart attack!"), which, in turn, provokes increased heart rate and fear (Clark, 1986). On the basis of the cognitive model, this feedback loop eventually culminates in a panic attack.

Certain generic features of networks signify *critical transitions*, which indicate that the system is approaching a tipping point (Scheffer et al., 2009). Identifying these telltale features could be of great value for clinical science, as mathematical models of such networks might predict remission or relapse and may, therefore, provide a critical window for early intervention to prevent relapse or even the onset of a disorder. In the aforementioned case of the patient with panic disorder who feared heart palpitations, it might be possible to predict the onset of a panic attack on the basis of the covariation pattern between frequent measurement points of the person's heart rate and catastrophic interpretations of these symptoms over a period of time.

One important feature that signals such a transition is *critical slowing down*, characterized by a network's slow recovery from local perturbations (e.g., due to external stressors). This suggests that the network has lost resilience and may therefore be tipped easily into an alternative state (e.g., from a normal state into a panic attack state). Indicative of slowing down are fluctuations in the configuration of the network (see Figs. 2D and 2F), measured by increased variance of changes of some elements of the network (e.g., moment-by-moment changes in heart rate in the case of the patient with panic disorder) and greater lag − 1 autocorrelations (see Figs. 2G and 2H; e.g., higher correlations of heart rate measured at times t and $t + 1$). Another example might be the change in a depression-prone student's social system after a move a new neighborhood. From a complex network perspective, the disturbance may be temporarily offset by the support of friends and family. However, this situation may worsen when academic stress increases, forcing the student to spend more time doing homework and thereby further limiting social contact. As a result, the stress in combination with social isolation may drive the system to a tipping point, cascading from the local perturbation to a systemic perturbation resulting in depression.

Predicting transitions in complex networks requires time series data with many high-resolution observations (e.g., changes in mood and other elements that are part of the depression network). In addition, it is often unclear what variables need to be observed and when. Several different parameters may be estimated to determine the presence of early warning signals of a critical transition. For instance, increases in autocorrelation, variance, and skewness betoken potential critical transitions (Carpenter & Brock, 2006; Dakos et al., 2012; Guttal & Jayaprakash, 2008; Scheffer, 2010). These would indicate a critical slowing down of the system (i.e., the state becomes more and more similar to the past state) and an increase in time spent near the *saddle point* (i.e., perturbations cause the system to become closer to the boundary that separates the two states; see Fig. 2). Estimates of these parameters, as well as inspection of their graphical properties, can facilitate interpretations about whether a critical transition may occur. A statistical package to predict critical transitions in complex systems has been developed by Scheffer and is called the Synergy Program for Analyzing Resilience and Critical Transitions, or SparcS. The program is freely available at http://www.sparcs-center.org/earlywarnings.html.

Especially valuable to clinical scientists will be the capability of identifying signals that predict transitions from nonpathological states to pathological states and vice versa. Experience-sampling methods have been used to accomplish this in studies of depression (Bringmann et al., 2013; Hartmann et al., 2015; Kramer et al., 2014; Telford, McCarthy-Jones, Corcoran, & Rowse, 2012; van de Leemput et al., 2014). However, only van de Leemput et al. (2014) have applied this method to examine the critical transition of the depression network in a large sample. The authors recruited 535 individuals from the general population and 93 depressed patients. To calculate early warning signals for the transition from the depressed state to the nondepressed state, the investigators had participants use experience sampling to rate their moods multiple times across 5 to 6 days. The data of the depressed patients came from two studies, which included baseline experience-sampling method measurements followed by an intervention (either a combination of pharmacotherapy and supportive counseling or allocation to a group receiving either imipramine or placebo) and follow-up assessments of depressive symptoms. The results pointed to critical slowing down as indicated by early warning signs of the onset and termination of depression (i.e., elevated temporal autocorrelation, variance, and correlation between emotions). This proof-of-concept study suggests that the complex network approach can be successfully applied to treatment-relevant issues.

A combination of idiographic and nomothetic network approaches was used by Fisher, Newman, and Molenaar

(2011) to examine treatment changes in the context of a dynamic network perspective within one specific diagnostic sample. Using EMA data, the authors examined 33 patients with generalized anxiety disorder who underwent psychotherapy. Idiographic data gathered through daily diaries of patients' anxiety were subjected to a spectral analysis, which enabled researchers to identify regular patterns of events (harmonic oscillations) in time series data that occurred at different frequencies. These idiographic data were then aggregated for nomothetic analyses of treatment outcome. The results showed that high-frequency power (power attributed to oscillations of 1 day or less) predicted treatment outcome, with less variance between these diary reports predicting better outcomes.

In summary, the analytic approaches described above reflect a subset of a growing number of statistical procedures for modeling complex networks. As indicated by Borsboom and Cramer (2013), longitudinal research will be vital to the advancement of complex network research, as the characterization of dynamic, temporal patterns in psychopathology will convey important information about how to optimize treatments. Moreover, the advent of new technologies will mitigate the burden associated with time-intensive research, such as experience-sampling methods, in which participants report thoughts, feelings, and symptoms at least daily. Although this requires the collection of a large amount of data over an extended period, the recent advancements in wireless-enabled wearable technology (e.g., smartwatches, smartphones) are likely to render this method feasible in the very near future.

Conclusion

The complex network approach offers an alternative to the latent disease model that assumes that symptoms arise from an underlying common cause. The network approach assumes that disorders exist as systems of inter-related psychological problems, including maladaptive behaviors, cognitive biases, emotional disturbances, and physiological abnormalities (Borsboom & Cramer, 2013; Hofmann, 2014, 2015). Although the empirical evidence is limited, this approach offers a fresh new perspective on understanding psychopathology. A complex network perspective on psychopathology not only addresses the comorbidity problem (Cramer et al., 2010) but also considers the functional connectivity between an individual's presenting problems. This, in turn, could have direct implications for therapy. Indeed, the complex network approach appears compatible with traditional and modern treatment approaches (Hayes, Yasinski, Barnes, & Bockting, 2015; Hofmann, 2014).

The patterns observed in treatment change, recovery, and relapse are consistent with the notion that complex systems can take on bistable states via critical transitions.

This makes a complex network perspective very relevant for clinical science. In highly connected networks relevant to mental health, transitions from one state to another are seldom linear. Rather, a change often occurs abruptly once the system reaches a tipping point. Longitudinal within-subject tracking of psychological problems will enable clinical researchers to identify critical transition points. However, this issue has seldom been discussed in the contemporary literature, with some exceptions (Fisher, 2015; van de Leemput et al., 2014). Adopting this approach would pave the way toward a personalized clinical science consistent with the National Institute of Mental Health's call for precision medicine for our field (Insel, 2013).

In conclusion, the complex network perspective provides an approach to elucidating causation in psychopathology that differs from traditional latent categorical and dimensional approaches. Traditional approaches hold that stressful life events, for example, cause the underlying condition of depression, which in turn causes the activation of symptoms that do not causally affect one another but simply reflect the condition's presence. The notion that sleep loss does not cause fatigue or concentration impairment is clinically implausible yet requisite for justifying inference to a latent common cause as the source of the problems. In contrast, the complex network perspective acknowledges environmental (and genetic) causes but as triggers activating individual features of a disorder, which, in turn, activate other elements of the network. Moreover, the arrow of causation may emerge as a self-reinforcing, homeostatic loop, such as hypervigilance fostering exaggerated startle responses in trauma survivors who, in turn, maintain their hypervigilance (see McNally et al., 2015). Unlike theoretical diagrams common in 20th century psychology (e.g., stimulus > organism > response models of neobehaviorism, causal flowcharts of cognitive psychology), the graphs produced by network analysis are empirically derived. Although most network research on psychopathology has involved computational procedures depicting correlational and partial correlational associations between elements of the network, these studies provide clues to possible causal relations confirmable in future longitudinal and interventional studies done within the complex network framework.

Note

1. Examples include psychological assessments (Heiby, 1995a, 1995b), neuroscience and genetics (Barabási, Gulbahce, & Loscalzo, 2011; Kim, Zhu, Chang, Bentler, & Ernst, 2007), and the social psychology of intractable ethnic conflicts (Vallacher, Coleman, Nowak, & Bui-Wrzosinska, 2010).

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