Ongoing and Future Challenges of the Network Approach to Psychopathology: From Theoretical Conjectures to Clinical Translations

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> I think the next (21st) century will be the century of complexity.
>
> Stephen Hawking (2000).

Introduction: Embracing Complexity Within Psychopathology

Over the past few decades, many scientific fields have changed the way they have sought to understand the world. Instead of attempting to reduce the complexities of their field into easy-to-understand models, they have instead embraced these complexities by mapping them out using networks (Barabási, 2012). This pursuit of complexity was enabled by both growing computational power (allowing more complex calculations on ever-larger datasets) and the development of network science. Network science contains key benefits that permitted its adoption by research fields as diverse as ecology, sociology, and epidemiology: (1) network science can apply to any type of system, with nodes representing the item under study (e.g., people, viruses, computers) and edges representing the connections between these nodes (e.g., correlations, temporal dependencies, probabilistic dependencies); and (2) network science grew out of graph theory,[a] allowing researchers to understand and predict networks using mathematical rules. Psychology researchers have also recently recognized the potential that network science generates for understanding psychopathology (for systematic reviews, see Contreras et al., 2019; Robinaugh et al., 2019a).

In this article, we first discuss how a network approach to psychopathology emerged and then review relevant network vocabulary and concepts. Afterward, we discuss the main tenets of a network perspective of psychopathology, as well as recent extensions of this perspective. We then evaluate network theory by discussing its current main challenges and future directions. Lastly, we consider the current and possible future clinical applications of a network perspective of psychopathology.

From a Latent Disease Model to a System-Based Approach

The understanding of mental disorders has for decades followed the medical disease model, where a single entity (usually conceptualized as latent, or unobserved, such as a still-undiscovered biological component) is assumed to be the common cause of symptom emergence and covariance (see **Fig. 1**A; for a discussion, see Fried, 2015). This parallels how medical diseases are understood: A malignant lung tumor explains the emergence and co-occurrence of symptoms such as chest pain and coughing blood, for

[a]Graph theory is the mathematical study of graphs, which are formal mathematical structures used to model pairwise relations between objects (definition from: https://mathworld.wolfram.com/GraphTheory.html).

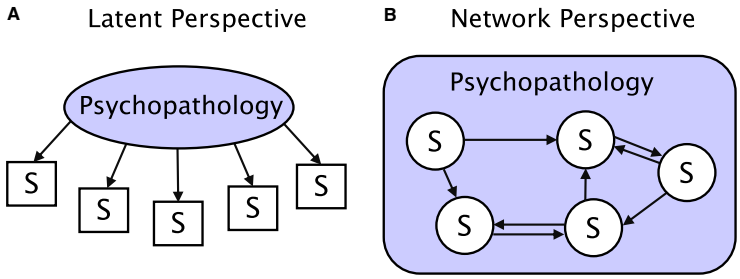


Fig. 1 A Latent vs. a Network Perspective of Psychopathology. Panel A: A latent perspective of psychopathology assumes that there is one main variable that causes all psychopathology symptoms. This model assumes that symptoms are interchangeable and independent. Panel B: A network perspective defines psychopathology through the causal interactions of its symptoms, where the symptoms activate and sustain one another. S = Symptoms. Inspired from P.J. Jones, A. Heeren, R.J. McNally, 2017. Commentary: a network theory of mental disorders, Front. Psychol, 8, p. 2.

example, in the same way that depression would supposedly explain why anhedonia, fatigue, and other symptoms co-occur (Borsboom and Cramer, 2013; McNally, 2016).

This common cause model of psychopathology contains important fallacies. First, in a medical model, the underlying causal disease can exist without symptoms (e.g., asymptomatic lung cancer). However, the idea of someone having a mental disorder without any symptoms is baffling, because symptoms are precisely how we define and diagnose mental disorders. Second, a crucial assumption of the common cause model is that all symptoms are interchangeable; specifically, because all symptoms arise from a common entity, they all have equal importance in determining a diagnosis (Fried, 2015). This assumption is not realistic for most mental disorders. Take depression as an example, wherein specific symptoms impact functioning in different ways and are differentially linked with various risk factors and biological correlates (Fried, 2015; Fried and Nesse, 2014; Kenneth, 2005). As another example, in the context of social anxiety disorder where fear and avoidance of social evaluative situations are the two hallmark symptoms, fear and avoidance are *not* interchangeable (for a discussion, see Heeren et al., 2020; Heeren and McNally, 2016). They are, instead, functionally distinct processes that merit different interventions, and merely relying on a sum score from a social anxiety questionnaire that aggregates fear and avoidance together would occlude this distinction (Heeren et al., 2020). Third, another important assumption of the common cause model is that all symptoms are independent from one another. Because a common entity causes them to arise, they do not influence each other (for further discussion of this assumption of local independence, see Borsboom, 2008; Holland and Rosenbaum, 1986). This assumption is also unrealistic for psychopathological symptoms. Both concentration difficulties and fatigue are symptoms of depression, for example, and it is clear that fatigue can lead to concentration difficulties and that insomnia may cause fatigue (Fried, 2015). Likewise, in anxiety disorders, fear may trigger avoidance, and vice versa (Heeren et al., 2020; Hofmann and Hay, 2018).

More generally, causal relationships between symptoms of mental disorders are consistently found, and these causal connections are at times even part of the diagnosis (Borsboom and Cramer, 2013). For instance, drawing on Mowrer's (1960) prominent two-stage learning theory, most diagnostic conceptualizations of anxiety disorders assume that avoidance symptoms—and use of safety behaviors in situations that the person cannot overtly avoid—directly trigger fear symptoms (e.g., Hofmann and Hay, 2018; for a discussion on the clinical relevance of distinguishing fear from avoidance, see also the seminal work of Rachman, 1978). All of these examples illustrate that a model assuming one common cause does not adequately explain the complexity of a mental disorder.

An alternate way of conceptualizing mental disorders is to view them as clusters of symptoms that tend to co-occur and co-vary across individuals. If similar clusters of symptoms co-occur regularly in different individuals, these clusters likely are not random but arise because their symptoms share a number of different causal mechanisms—a notion known as mechanistic property clusters (Kendler et al., 2011). Researchers and clinicians have grouped symptom clusters and named them as syndromes including, for example, major depressive disorder, social anxiety disorder, and bipolar disorder. Nonetheless, it is still crucial to examine these syndromes at a symptom level, because different people with the same diagnosis often exhibit different specific symptoms (Fried and Nesse, 2015), and because the symptoms often interact and reinforce one another, potentially becoming a vicious cycle (Borsboom and Cramer, 2013). Thus, to be able to understand how people develop and experience psychopathology, it is necessary to understand how symptoms influence and interact with one another. A key way to investigate symptom interactions involves visualizing and modeling mental disorders as networks of symptoms.

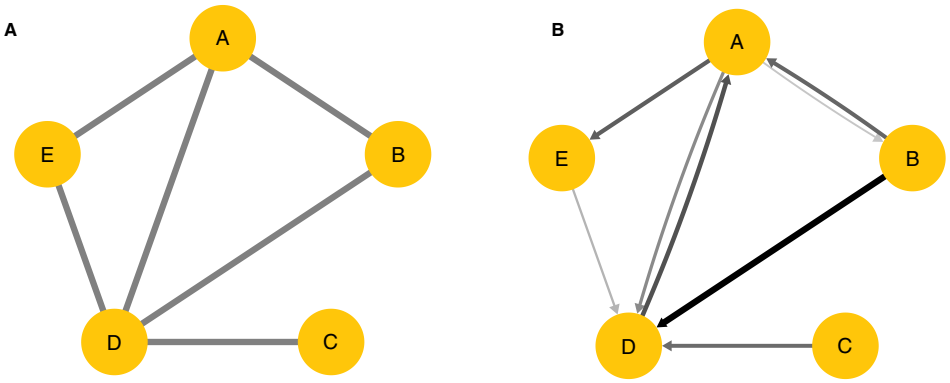
A Network Perspective of Psychopathology

Psychology researchers have leveraged network science to build a network theory of psychopathology that addresses the fallacies of the latent disease model and extends our understanding of mental disorders. Instead of focusing on mental disorders as something concrete and specific, a network approach visualizes symptoms as nodes and maps out the associations between them. This emphasis on the interactions of symptoms shifts the focus from how to precisely define the boundaries of a disorder to how

symptoms activate and sustain each other, and ultimately provides clues about how the network is self-sustaining. This reveals how network theory defines psychopathology—as (self-sustaining) networks of causally interacting symptoms (see **Fig. 1**B). Psychology seeks to understand what causes symptoms, and this also is true of network theory. Network theory posits that symptoms cause (or, in other words, activate or inhibit) each other, through feedback loops and other interactions. To assess whether the interactions between nodes are in fact causal requires meeting many assumptions, such as including all relevant variables in the network, establishing temporal precedence, or investigating conditional independence (i.e., the association remaining between two nodes after controlling for their association with any other nodes; Epskamp and Fried, 2018). Most network analyses, therefore, investigate interactions between nodes that are *indicative* of causality, requiring either experimental research designs or extensive replications with full adherence to assumptions to make firm conclusions regarding causality[b] (Epskamp et al., 2018b).

Network Models: A Brief Vocabulary Lesson

Before discussing how network analyses can be applied to psychopathology, we will begin by reviewing some of the essential vocabulary and concepts of network science (for a thorough coverage of network science, see Barabási, 2016). A network is a graph that, together with a function, assigns a real number to each connection. A network analysis, for its part, issues a network to visualize and understand a system; that is, it traces out the connections between the system components (see **Fig. 2**). The components (which can be any object, person, etc.) are called nodes, and the connections between nodes are called edges. A vast variety of systems can be conceptualized as a network. Examples range from a power grid (with generators as nodes and power supply lines as edges), to the world wide web (with webpages as nodes and their links toward one another as edges), to neural networks (with neurons as nodes and their connections as edges), to social networks (with people as nodes and their personal or professional ties as edges).



C

Nodes	A	B	C	D	E
A	0	1	0	1	1
B	1	0	0	1	0
C	0	0	0	1	0
D	1	1	1	0	1
E	1	0	0	1	0

D

Nodes	A	B	C	D	E
A	0	0.22	0	0.45	0.62
B	0.59	0	0	0.98	0
C	0	0	0	0.57	0
D	0.67	0	0	0	0
E	0	0	0	0.29	0

Fig. 2 Example Networks and Their Adjacency Matrices. Panel A: A network that is undirected (bidirectional connections) and unweighted (edges are binary, either present or absent). The circles represent nodes, and the lines represent edges. Panel B: A network that is directed (with edges that point from one node to another) and weighted (the edges vary in strength between 0 and 1, and this strength is reflected in width of the edge. Panel C: The adjacency matrix that accompanies **Fig. 2**A. Each value records the edge weight that connects the specified two nodes. All edge weights are either 0 or 1 since **Fig. 2**A is an unweighted network. Panel D: The adjacency matrix that accompanies **Fig. 2**B. The edges vary from 0 to 1, with larger values represented in **Fig. 2**B with thicker lines. The adjacency matrix is not symmetrical (unlike **Fig. 2**C) since if an edge points from node A to node E, it is just represented once in the adjacency matrix. The R code used to estimate and visualize these two networks has been made publicly available via the Open Science Framework. Source: https://osf.io/njsf6/.

[b]We discuss "causal" connections and interactions between symptoms throughout this article. Following Borsboom (Borsboom, 2017), we use the term causal in the sense of interventionist theories of causation, where intervening (through experimental or natural means) to change the state of one symptom would change the probability distribution of its connected symptom(s).

Networks have a number of different characteristics. First, networks can be either directed or undirected. In an undirected network (see **Fig.2**A), edges represent bidirectional links, whereas in a directed network (see **Fig. 2**B), the edges point from one node to another. Second, networks can also be weighted or unweighted. In unweighted networks (see **Fig. 2**A), edges are binary (i.e., either present or absent), while in weighted networks (see **Fig. 2**B), each edge has a specific strength or weight, which is usually reflected by the width of the edge (i.e., thicker edges represent stronger connections). An adjacency matrix encodes all edge values within a network such that each node is represented by a column and a row in the matrix, and the weight of each edge can be found at the intersection of the two relevant nodes (see **Fig. 2**D). If the network is unweighted, the edge weights will be encoded as 1 for present and 0 for absent (see **Fig. 2**C).

A network representing a mental disorder is typically weighted, since symptoms form the nodes and the connections between symptoms are not known but estimated (such as through correlations, partial correlations, or other methods). Psychopathology networks can be based on either cross-sectional or time-series data. If the network is estimated using cross-sectional data, this data is collected at one time point, usually made up of self-report questionnaire responses. Cross-sectional psychopathology networks allow researchers to visualize and better understand how symptoms are generally related to each other, by mapping the correlations (or other statistical relationships) between symptoms. These networks are typically undirected, because cross-sectional data yields no information on how symptoms influence each other over time. A dominant estimation method is the Gaussian graphical model (GGM), which visualizes partial correlations between nodes. GGMs usually employ a regularization method to render the model sparse or, in other words, to only include edges that likely represent true connections (Epskamp et al., 2018c). There are a number of tutorials that explain how to estimate cross-sectional psychopathology networks using R code (e.g., Costantini et al., 2015; Epskamp et al., 2018a; Epskamp and Fried, 2018). More advanced methods, such as directed acyclic graphs (DAGs)[c] and relative importance networks,[d] allow researchers to model directed networks using cross-sectional data. Although DAGs (for illustrations, see Heeren et al., 2020; McNally et al., 2017) and relative importance networks (for illustrations, see Heeren and McNally, 2016; Robinaugh et al., 2014) have occasionally been used in clinical psychology, they have increasingly become popular in other fields, such as epidemiology and environmental sciences.

Psychopathology networks can also be constructed from time-series data, collected, for example, through experience sampling methodology where participants answer short questions once or multiple times a day over weeks. These temporal networks are typically estimated using multilevel autoregressive (VAR) models (Bringmann et al., 2013, 2016), although there are other possibilities, such as group iterative multiple model estimation (Beltz and Gates, 2017) or sparse VAR models (de Vos et al., 2017). Networks estimated from temporal data result in directed networks that represent how symptoms influence one another over time. They require many timepoints but fewer participants than cross-sectional networks. With sufficient timepoints, a directed network can even be estimated using the data from just one person, yielding a personalized (or idiographic) network (e.g., Fisher et al., 2017).

Centrality

Using network theory to model psychopathology allows the adoption of network tools and graph theory concepts to understand mental disorders. One of these network concepts is node centrality, which posits that some nodes in the network are more important to the network structure than others. Nodes are considered more central if they are especially connected to the rest of the network (i.e., connected to many nodes), because they can then influence the entire network. As an example, picture a network tracing out how people gossip. If someone frequently gossips with other people, they form a central node in the network. If they share a specific story, it will quickly spread throughout the network. On the other hand, if someone gossips only with one or two people, they are represented by a node with few connections. If this person shares a story, it will only gradually spread throughout the network and might even remain limited to a small part of the network. Another example involves virus propagation: someone who sees many people in a day (i.e., very connected to other people) will, if infected, spread the virus to many more people than someone who sees only one or two people in a day.

A variety of centrality metrics exist, all using slightly different methods to indicate how connected a node is to the rest of the network (for an overview of different centrality indices, see Borgatti, 2005; McNally, 2016). Commonly used centrality metrics in psychopathology networks include strength (or degree) centrality (McNally, 2016), which computes the sum of absolute edge weights connecting to a node, and expected influence, which operates similarly while also taking into account the negative or positive valence of the edge (Robinaugh et al., 2016). There are many other common centrality metrics, including betweenness centrality (how many times a node lies on the shortest path connecting two other nodes) and closeness centrality (the average distance from one node to all other nodes), both of these indices involve assumptions that are very unlikely for psychological variables (Bringmann et al., 2019).

[c]Directed acyclic graphs (DAGs) encode the conditional independence relationships and characterize the joint probability distribution of the variables. DAGs can thus be decomposed as a product of the conditional distribution of each node given its parent nodes in the graph, thus rendering DAG analysis capable of indicating whether the presence of node A probabilistically implies the presence of node B more than vice versa (for more details regarding the logic behind the use of DAGs, see Pearl, 2009).

[d]Relative importance denotes the proportionate contribution that each predictor makes to R^2, considering both its direct effect (i.e., its correlation with the criterion) and its effect when combined with the other model variables in the regression equation (Johnson and Lebreton, 2004). The relative importance metric ranges from 0 to 1, and quantifies the amount of explained variance attributable to each predictor after controlling for multicollinearity (Johnson and Lebreton, 2004). The resultant relative importance network is both weighted and directed with arrows signifying the direction of prediction, not causality.

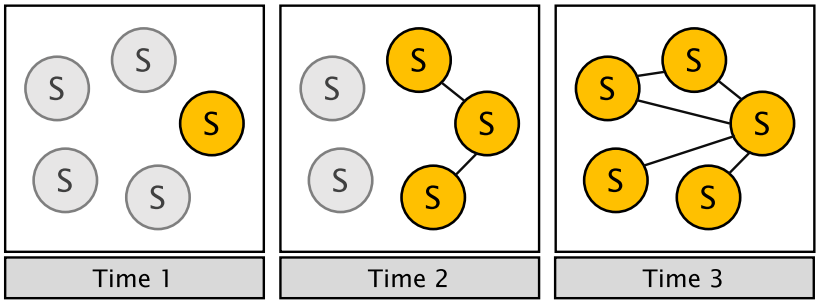


Fig. 3 A Central Node Activating Other Nodes. Central symptoms have many connections to the rest of the network, and the mathematical theory of preferential attachment (Barabási and Albert, 1999) posits that when new nodes are activated, they connect to central nodes first. This figure provides an illustration of how this might occur. S = Symptoms.

When interpreting node centrality through the lens of psychopathology, researchers posit that central symptoms are especially important to the course of the disorder, since if a central symptom is activated, it is more likely to activate and influence other symptoms (see **Fig. 3**). This also adheres to the mathematical theory of preferential attachment, which posits that when new nodes are activated, they connect to central nodes first (Barabási and Albert, 1999). The concept that central symptoms are key to the course of a disorder is termed the *centrality hypothesis* (Borsboom and Cramer, 2013). The centrality hypothesis offers new avenues for research into how disorders develop and persist because it posits that central symptoms activate and sustain other symptoms, thus playing a key role in the etiology and maintenance of disorders. This also proposes central symptoms as candidates for prevention and treatment efforts, since if a clinician can "turn off" or downregulate a central symptom, then other symptoms are less likely to be activated or sustained (McNally, 2016).

On an empirical level, multiple studies have investigated whether centrality indices actually identify symptoms that play a role in the course of a disorder. In their systematic review, Robinaugh et al. (2019a) report that such studies have found that central symptoms are more predictive of a later diagnosis than peripheral symptoms and that central symptoms are highly correlated with change in the rest of the network. But, Robinaugh and colleagues also caution that the results from these studies—which all include the same measures in both the baseline and the subsequent timepoint—could also be explained by a common cause model. In this case, nodes that are identified as central symptoms in a network analysis would represent more reliable indicators (i.e., they would contain less measurement error), which would be more predictive of future psychopathology than less reliable indicators. A few recent studies present evidence that cannot be accounted for by a common cause model, however. Elliot et al. (2019) found that central anorexia symptoms at baseline were strongly correlated with recovery status and posttreatment clinical impairment prognostic utility. Since clinical impairment was measured independently from the symptoms included in the network, this presents more robust evidence for central symptoms influencing the course and recovery of a disorder. Likewise, Spiller et al. (2020) found that in a large sample of PTSD patients, only expected influence (and not other centrality estimates) predicted the association between changes in a node and changes in the entire network (presumably indicating a node's importance to the network's activation) in two different PTSD measures. However, other non-centrality metrics such as mean symptom severity yielded stronger predictions than expected influence. Evidence regarding the causal role of central nodes remains therefore decidedly mixed.

All studies presented above suggest only correlational associations between central symptoms and later psychopathology outcomes. As Spiller et al. (2020) emphasize, to assume a causal role for central nodes implies that these nodes causally interact with other nodes over time and within individuals; investigating the centrality hypothesis mainly with cross-sectional between-subject networks is therefore a major limitation. To obtain robust evidence for the centrality hypothesis and its implications requires an experimental paradigm, one targeting and manipulating specific central nodes (vs. peripheral nodes) and then examining how the network flow changes. If the centrality hypothesis (and its implications for clinical treatment) are supported, then downgrading a central node through some sort of intervention should lead to the entire network becoming less active (and vice versa for upgrading a central node). Targeting a peripheral node, on the other hand, should have a much lesser effect on the network.

These strong clinical predictions arising from the centrality hypothesis implicate many assumptions, such as whether one can even target a specific node on its own without also affecting other nodes (Bringmann and Eronen, 2018). There also is no universally-accepted centrality metric, and the implications and interpretations of centrality metrics are not straightforward (Bringmann et al., 2019). Most centrality metrics were developed for social networks, which have people as nodes and their relationship, such as gossip partners as in the example above (or sharing an article authorship, being classmates, etc.) as edges (Bringmann et al., 2019). These centrality metrics were developed under several assumptions that are problematic for psychopathology networks. One example is that the edges in social networks are often already known; specifically, the raw data already includes the relationships between people. With psychopathology networks, however, the edges are estimated, since the raw data do not include information on how symptoms relate to one another (Bringmann et al., 2019). Another unlikely assumption involves nodes being exchangeable; specifically, one person that has X number of connections plays the same role in a gossip network as another person who has the same number of connections. In psychopathology networks, however, nodes could have the same number of connections

but represent symptoms of varying severity (e.g., suicidal thoughts vs. fatigue), and it could be problematic to assume they have the same impact on network functioning (Bringmann et al., 2019). Despite these limits, methods now exist to estimate the stability of centrality indices (Epskamp et al., 2018a), but only for cross-sectional networks and not temporal ones.

Connectivity

Another important network concept is connectivity, which refers to whether the overall network includes many connections (meaning its nodes are closely connected) or few connections (meaning its nodes are relatively independent and isolated). In general, if a network is more connected, then activation or information will spread through the network more quickly. Considering the previous example of a gossip network again, if most people in the network frequently talk to many other people, then gossip will rapidly spread throughout the network. If, however, the network is not strongly connected, and most people only gossip seldomly and with few individuals, then it will take longer for specific stories to reach everyone in the network. Different researchers have used different ways to measure connectivity, including the number of edges (as a ratio over the number of possible edges; de Vos et al., 2017) and the average of the absolute values of edge weights (Bringmann et al., 2016).

Within psychopathology networks, researchers have posited that the overall network connectivity is linked with severity. If a network is more densely connected, then it is more likely to be or to become pathological (Borsboom, 2017). This relies on the assumption that in a more connected network, activity will spread throughout the network more quickly, and symptoms will activate each other more easily and influence each other more. Borsboom and Cramer (2013) likened a network with high connectivity to a set of dominoes lined up close together, such that if one domino goes down (or one node is activated), it sparks a cascade of dominoes falling down (or a cascade of node activation). The notion that symptom networks that are highly connected are likely to be more severely pathological (or more at risk for developing psychopathology) is termed the *connectivity hypothesis*.

At the empirical level, there has thus far been mixed support for the connectivity hypothesis. In their systematic review, Robinaugh et al. (2019a) identified a number of cross-sectional analyses that investigated connectivity through group comparisons. Different methods include comparing people with a mental disorder to those without (e.g., Heeren and McNally, 2018), comparing the baseline measures for groups whose symptoms either persisted or remitted (e.g., Van Borkulo et al., 2015), and investigating connectivity before and after treatment (e.g., Bryant et al., 2017). Robinaugh et al. (2019a) concluded that greater connectivity usually accompanies greater psychopathology severity (e.g., a diagnosis); but, they found mixed results for the other comparisons. Investigating connectivity in cross-sectional networks presumes that connectivity is linked with severity at a group level, while it is possible this only occurs on an intra-individual level. Temporal networks can solve this uncertainty, since they allow investigations into intra-individual network dynamics. A number of studies investigating connectivity in mood state networks have found that increased connectivity accompanied increased severity (Bringmann et al., 2016; Hasmi et al., 2017).

The connectivity hypothesis rests on the assumption that increased connectivity indicates the presence (or likelihood) of feedback loops which sustain symptoms; but, many questions still remain regarding how best to examine connectivity. For example, psychopathology networks often include both positive and negative edges. If symptoms (or other contextual components) inhibit one another (as negative edges indicate), does connectivity still imply a self-sustaining vicious cycle? There are also many questions about how to compute connectivity (for discussion, see de Vos et al., 2017). For example, should researchers include only positive edges, or only negative edges, or both (e.g., Bringmann et al., 2016)? Should they compute either inter-node connections, or intra-node connectivity (i.e., autoregressive feedback loops), or both (e.g., Groen et al., 2019)? And, should they include only significant edges, or all edges (e.g., de Vos et al., 2017)? These questions are currently unanswered, and more research is required to determine how these considerations affect the connectivity hypothesis. In light of this uncertainty, researchers should follow the example of de Vos et al. (2017) and include multiple data preprocessing and estimation choices to examine how these affect their results. Future research can also go even further and conduct multiverse analyses, where a multitude of datasets are constructed from the many alternative data processing choices and analyses are conducted on each dataset (Steegen et al., 2016).

The literature on the connectivity hypothesis is still rather limited, especially regarding studies that investigate connectivity using temporal networks. Through this brief overview of that literature, it should be obvious that substantial work remains to determine how preprocessing and analytic choices affect results and interpretations. Nonetheless, the connectivity hypothesis proposes a novel approach to understand and investigate psychopathology severity, by focusing on how symptoms relate and interact with one another. Some researchers also advocate for additional investigations into connectivity that go beyond the connectivity-as-vulnerability hypothesis (Groen et al., 2019), such as by pursuing questions that arise from the complex dynamical systems theory literature (for an overview, see **Comorbidity** on critical transitions).

Comorbidity

With its focus on symptom-to-symptom connections, network theory proposes an intuitive understanding of comorbidity (i.e., dual or multiple diagnoses). Comorbidity has long interested and puzzled psychologists, especially because the rates of comorbidity are high. For people who have one diagnosis, around 45% meet the criteria for another diagnosis as well (Kessler et al., 2005). Under a disease model of psychopathology, which conceptualizes disorders as distinct entities with strict boundaries, attempting to understand why and how people have multiple disorders is a complicated endeavor. Theories of comorbidity range from statistical artifacts arising from the construction or measurement of disorders (i.e., large overlaps in symptoms for many disorders in the *Diagnostic and Statistical Manual of Mental Disorders*), to actual underlying connections between two latent disorders (such as through

a common etiological mechanism), to the existence of a "*p* factor" (i.e., a general factor predisposing people to psychopathology analogous to the general *g* factor for intelligence; Caspi and Moffitt, 2018; Cramer et al., 2010). However, investigating comorbidity by focusing on diagnoses, as suggested by the disease model of psychopathology, makes little sense because the boundaries between disorders are rather blurred (Cramer et al., 2010).

Network theory, on the other hand, offers a straightforward explanation for how people develop comorbid disorders. Because network theory defines a disorder through its symptom-to-symptom connections, comorbidity would occur through common connections that bridge disorders. These common connections can operate through overlapping symptoms or symptom-symptom connections that exist in the co-occurring disorders, but also through symptoms that connect them to the same process (Cramer et al., 2010). Symptoms which build a path from one disorder to another are also called bridge symptoms. Borsboom and Cramer (2013) give the example of how chronic worry (a main symptom of generalized anxiety disorder) can lead to sleep problems and thus fatigue, both of which are simultaneously symptoms of generalized anxiety disorder and depression. Sleep problems and fatigue, in turn, can then lead to depressed mood, which is a main symptom of depression. This example demonstrates how pathways that connect symptoms of a disorder to one another can also lead to the activation of symptoms from a comorbid disorder; specifically, symptoms do not stop interacting just because they reach a theoretical diagnostic threshold. The focus of network theory on symptoms and their connections allows intuitive investigations into comorbidity that explicitly recognize the blurry boundaries separating mental disorders.

On an empirical level, studies regularly find that symptoms of one disorder are differentially related to symptoms of another disorder (e.g., Bekhuis et al., 2016), supporting a perspective of comorbidity that focuses on symptoms rather than on syndromes. In line with this, studies utilizing network approaches to investigate comorbidity often focus on identifying symptoms that bridge two disorders. This can be done with centrality indices that specifically measure *bridge centrality* (i.e., how well-connected a node is with symptoms of another disorder; Jones et al., 2019). A specific example includes an investigation into the comorbidity of social anxiety disorder and depression (Heeren et al., 2018a). This investigation identified suicidal ideation, loss of interest, and anhedonia as depression symptoms closely connected with social anxiety disorder, while avoidance of participating in small groups and avoidance of attending parties were symptoms of social anxiety disorder closely connected with depression. Another study investigated comorbid anxiety and eating disorders (ED) and found that avoidance of social eating had the highest bridge centrality among ED symptoms, while low self-confidence had the highest bridge centrality among anxiety symptoms (Forrest et al., 2019). Another way to investigate comorbidity with network analyses uses directed acyclic graphs, a Bayesian approach that generates directed networks from cross-sectional data (see "**Network Models: A Brief Vocabulary Lesson**" on network vocabulary). Researchers using this approach have identified nodes that seemingly drive activation of both disorders and have labeled these as *probable bridge symptoms* (McNally et al., 2017).

In all of these studies, the researchers discuss how the identified bridge symptoms could be ideal targets of prevention efforts that seek to prevent someone with one disorder from developing a comorbid disorder, or targets of treatment efforts that seek to successfully consider both (or multiple) comorbid disorders. To give a specific example, Levinson et al. (2018) identified difficulty with public eating and drinking as a symptom bridging social anxiety and eating disorders. They suggested that future clinical investigations should examine whether exposure therapy that specifically targets public eating and drinking beverages (vs. targeting other non-bridge symptoms) can decrease symptoms for both social anxiety and eating disorders.

These clinical possibilities are intriguing; but, extensive research is needed to establish the validity and effectiveness of any clinical applications that target bridge symptoms. For one thing, there are still relatively few network investigations into comorbidity, and no replications have yet been conducted to verify the results of any of the above studies in different samples. For another, clinical trials are required to evaluate whether targeting bridge symptoms is actually effective (and/or more effective than existing interventions) in treating and preventing comorbid disorders. Moreover, there is not yet a concrete understanding of how exactly bridge symptoms might affect comorbidity (Cramer et al., 2010). For example, do specific bridge symptoms increase the risk of developing a comorbid disorder when compared to other (non-bridge) symptoms? Does intervening on bridge symptoms in people with comorbid disorders lead to slower symptomatology for both disorders, or prevent the development of further comorbidity? Answering these types of questions would further clinical knowledge regarding comorbidity, and arriving at these answers requires experimental study designs. Nonetheless, the network approach, even in its current form, is useful for investigating comorbidity, as it allows researchers to examine how symptoms interact regardless of the boundaries of a diagnosis (Fried, 2015). Specific recent developments in bridge centrality metrics (i.e., Jones et al., 2019) also allow researchers to easily identify potential bridge nodes, which can help researchers piece together which symptoms seem especially relevant in connecting two (or more) comorbid disorders.

Network Changes: Critical Transitions

Prior to the development of network theory, there were already branches of systems science that conceptualized mental disorders as complex dynamic systems (e.g., Hayes and Strauss, 1998). Network theorists have thus adopted some of the approaches and analytic methods of system science to investigate psychopathology networks (for a brief overview, see Robinaugh et al., 2019a). One specific example involves examining how and predicting when a complex system transitions from one state to another. This has been researched in climate science, ecosystems, and other fields (Scheffer et al., 2009). Investigating and predicting transitions between stable states can also be highly useful to psychopathology research, such as when viewing "healthy" functioning as one stable state that can transition into a state of psychopathology, or vice versa (Borsboom, 2017; Hayes et al., 2015). Complex

systems usually provide early warning signals when they are on the brink of tipping into a new state. Recent research has identified one such warning signal as *critical slowing down*—the system as a whole becomes more synchronized, with its components showing high variance and high autocorrelations (for a more detailed explanation, see Scheffer et al., 2009). Psychology researchers have hypothesized that when individuals approach a tipping point from a healthy state to a depressed state, this transition is also preceded by a critical slowing down of the psychological system (Van De Leemput et al., 2014).

On an empirical level, few studies to date have investigated critical transitions in psychopathology. Researchers have found support for critical slowing down preceding a transition from a healthy state to a depressed state, in both group-level (Van De Leemput et al., 2014) and individual (Wichers et al., 2016) data. Others have identified critical slowing down in two specific affect variables (i.e., feeling "alert" and "inspired") that predicted greater changes in depression symptoms over time (Curtiss et al., 2019). Phase transitions can also be investigated within a disorder, for example to clarify the transition pathways from a depressive episode to a manic episode in bipolar disorder. Nakamura et al. (2013) found evidence that critical slowing down of mood fluctuations and physical activity predicted a transition from depression to hypomania in one patient.

Of the few studies that have thus far investigated critical transitions in psychopathology networks, most have focused on depression. Therefore, extensive further research is required to draw robust conclusions about whether early warning signals can reliably indicate a transition into (or out of) a state of psychopathology, and whether this is limited to specific psychopathology states (such as depression) or applies more widely to other forms of psychopathology. More research is also required to ensure that the indices used to investigate early warning signals (e.g., autocorrelation or variance) are reliable. With additional theoretical validation and methodological robustness, important clinical implications arise. For one thing, this will allow psychology researchers to better identify general early warning signs that signal a tipping point into psychopathology or recovery (e.g., Curtiss et al., 2019), and then strategically use these signs in targeted treatment approaches. Being able to detect early warning signals for transitions involving psychopathology states could also improve when and how treatment (or prevention) efforts are implemented, on both a general (Van De Leemput et al., 2014) and an individualized level (e.g., Wichers et al., 2016).

Extensions of Network Theory

Beyond Symptoms

The original iterations of network theory mostly focused on networks comprised solely of psychiatric symptoms (e.g., Borsboom, 2017); but, the emphasis on causal interactions between symptoms propelled other researchers to include any variables that had a plausible causal role within the system, whether formally recognized as symptoms or not (Jones et al., 2017). To draw conclusions about causal connections, a key assumption involves including all relevant variables in the model (Epskamp et al., 2018b), and it is likely that relevant variables are not limited to DSM-recognized symptoms. This has led some researchers to include psychological processes of mental disorders, as studied with laboratory measures in experimental psychopathology, as nodes in psychopathology networks. For example, Heeren and McNally (2016) included as nodes theory-driven cognitive and behavioral mechanisms (i.e., attentional bias for threat, attention control, emotional reactivity to a laboratory-induced stressor, behavioral avoidance) thought to be involved in the maintenance of social anxiety disorder. They found that the orienting component of attention as well as avoidance were central nodes in the network structure. As another example, Everaert and Joormann (2019) included nodes representing repetitive negative thinking and positive reappraisal, two emotion regulation strategies, in a network of depression and anxiety symptoms. They found that repetitive negative thinking had high bridge centrality, and so played a large role in the comorbidity between depression and anxiety symptoms. In today's literature, the use of network analysis to examine the "bridges" between psychopathology symptoms and psychological processes thought to be involved in psychopathology has become one of the most fruitful research agendas, given that it generates an especially strong enthusiasm by the community of clinical psychological researchers (e.g., Heeren et al., 2020; Kraft et al., 2019; Weiss et al., 2020).

Allowing networks to include more than just symptoms also paves the way for networks that go beyond symptoms, and researchers have started to investigate how features of different transdiagnostic phenomena thought to be involved in psychopathology interact together. For instance, Bernstein et al. (2017) relied on a network approach to investigate how features of executive control interact with features of rumination. Likewise, Greene et al. (2020) recently examined the interplay between features of maladaptive daydreaming and emotion regulation strategies. Furthermore, others have even started to embrace a network perspective to examine how the constitutive components of a given transdiagnostic phenomenon interact together. For instance, Bernstein et al. (2019) proposed reexamining trait rumination—a core transdiagnostic process thought to be involved in the etiology and maintenance of several mental disorders—as a network system of interacting components (i.e., nodes). In the same vein, Heeren et al. (2018b) offered a network approach to trait anxiety—a key transdiagnostic mechanism of anxiety and related disorders.

Other Psychological Phenomena

A network approach has not been limited to psychopathology; indeed, it has also been applied more broadly to a variety of psychological phenomena. Adopting a network approach encourages novel theoretical conceptualizations that focus on component-level interactions, as well as new statistical tools and visualizations. To go into detail about how a network approach can bring new theoretical understanding to a field of study, we will focus on personality research (Cramer et al., 2012). A traditional latent view of personality posits that personality dimensions are latent constructs which cause the items they measure; for example, being

extraverted causes a person to like attending parties. A network perspective instead posits that the way people act and feel influences the way they think about themselves, and some of these behaviors and feelings naturally cluster together (such as "feeling comfortable starting conversations" and "liking parties"). When modeling these various personality components in a network, the network architecture then reveals clusters that can be interpreted as personality dimensions. Previous theorists have critiqued the latent model of personality as incompatible with the way specific personality components dynamically interact with their environments. A network approach offers an alternative theory of personality (with accompanying methodological and analytical techniques), where personality dimensions consist of the gradually consolidated and subsequently maintained interactions between the way people act, think, and feel within specific environments.

Researchers have similarly applied network analysis to intelligence, using it to unite models of cognition and intelligence by positing that the cognitive system develops mutually with different facets of intelligence (Van Der Maas et al., 2017). Network science has also been used to formalize a theory of attitudes, tying together the interactions between beliefs, feelings, and behaviors in a way that promotes testable predictions (Dalege et al., 2016). Network analyses have even been proposed as a useful tool for explaining functional disorders (e.g., fibromyalgia, chronic fatigue) because a focus on symptom interactions makes sense given the lack of unique pathophysiology and large individual differences in symptom patterns (Hyland, 2019). In addition, using network analysis to conceptualize functional disorders allows intuitive metaphors that patients appreciate, such as viewing functional disorders as "programming errors" that arise from a complex biological and behavioral system (Hyland, 2019).

In general, a network approach to psychological concepts discards a common cause explanation and instead proposes that psychological phenomena arise from an interactive system of components. As such, a network approach always prioritizes investigations at the component-level instead of focusing on the phenomenon as a whole (Bringmann and Eronen, 2018), which can be useful to reconceptualize research and theory for a variety of psychological fields of study.

Extending Inwards to Biology and Outwards to Social Context

When considering disorders as causally interacting networks, it is clear that symptoms and psychological phenomena do not interact in isolation but always within a context (Borsboom and Cramer, 2013). This context is first and foremost located within a biological system, our human bodies. When someone feels lethargic, or cries, or feels anxious, a whole host of biologically-based components are at play, from hormones to neurotransmitters to protein chains to genes. Extensive research has concluded that a singular biological component is never solely responsible for how a person experiences feelings, emotions, or behaviors (Kendler, 2005). This is also true on a broader level. Even phenomena that are thought as purely biological—such as diseases—are typically much more complicated than a single genetic abnormality (Barabási et al., 2011). Indeed, medical research has embraced network science, because it allows investigating diseases as complex intracellular networks that interact with other (internal and environmental) systems (Barabási et al., 2011). This has prompted Guloksuz et al. (2017) to argue that the strict dichotomy between medical diseases and mental disorders, which motivated the adoption of a network approach to psychopathology, should be relaxed.[e] They propose that the main difference between medical diseases and mental disorders is that researchers have identified more of the biological components involved in disease networks, while psychopathology networks still remain mostly at the level of behavioral and affective signs and symptoms (Guloksuz et al., 2017).

These psychological symptoms are also located within an external environment. Humans are embedded within a social context and interpret their experiences through that social context. The most immediate social context is an individual's family, and family systems theory asserts that an individual's behaviors and feelings, as well as any psychological symptoms, are always in conversation with an interpersonal context (Bavelas and Segal, 1982). Indeed, humans do not exist in isolation but are constantly acting and reacting to their environment—not only immediate environments such as the family, workplace, or school, but also broader environments such as the neighborhood, media, and social services, and macro-level contexts such as culture (Bronfenbrenner, 1979). Bronfenbrenner's varied ecological contexts have even been recently theorized as overlapping and interconnected networks, where various social interactions in different contexts together shape an individual's development and expression (Neal and Neal, 2013), including the way they express psychopathology symptoms.

Oude Maatman (2020) discusses in depth how specific network connections can vary according to the cultural and historical context within which they are embedded. As an example, he considers the connection between loss of honor and suicidal ideation. In WWII-era Japan, a loss of honor was a reason to consider committing suicide, as suicide was the only way to regain honor. For a devout Catholic, however, the connection is traditionally the opposite, with suicide representing a gateway to hell and something to avoid at any cost. In both cases, the cultural context can determine what connections are made between mental states. These connections could be automatic (formed through neural plasticity) or cognitive (such as if thinking about loss of honor naturally leads to thinking about suicide). In either case, this example demonstrates that culture can structure how mental states are causally connected within individuals. As such, researchers should consider including cultural contexts as factors in network analyses when relevant to the network in question.

Symptoms—and, more broadly, any psychological processes—are inextricable from their contexts, from the biological level up to the cultural level. This supports extending psychopathology networks to include the contexts of disorders. A few network studies have already begun to combine psychological networks with contextual components. For example, a network analysis of positive

[e]The strong binary opposition between latent models and network models has similarly been questioned, as latent and network models can both be used without assuming that their models represent causal connections (Bringmann and Eronen, 2018; van Loo and Romeijn, 2019), and models now exist that combine network and latent components (Epskamp et al., 2017).

and negative affect in bipolar disorder included actigraphy measures of physical activity (Curtiss et al., 2019), while another study investigated the connections between affective states, genetic vulnerability to psychopathology, and childhood trauma (Hasmi et al., 2017). One network study investigated how psychotic experiences and momentary affect interacted with minor daily stress and being alone (Klippel et al., 2018), while another study examined how social media use co-varied with depressive symptoms (Aalbers et al., 2018). A third study examined how COVID-19-related worries and beliefs in the exaggeration of its threat interacted with avoidance and coping behaviors (Taylor et al., 2020), and another investigated how parental burnout interacted with family-related variables (Blanchard et al., 2021; for a discussion, see Blanchard and Heeren, 2020). These examples highlight how the larger, ongoing efforts of the field to incorporate contextual variables and investigate how symptoms vary in relation to their inner and outer environments fulfill an especially valuable and useful niche in clinical psychology.

The future possibilities of contextual networks expand even further. Guloksuz et al. (2017) propose the concept of layers of networks, with each layer situated at a different level of analysis. For example, a layer of biological components would be embedded within a layer of signs and symptoms, embedded within a layer of social interactions and environmental factors, embedded within a layer of cultural and historical context (see **Fig. 4**). While nesting network analyses within different

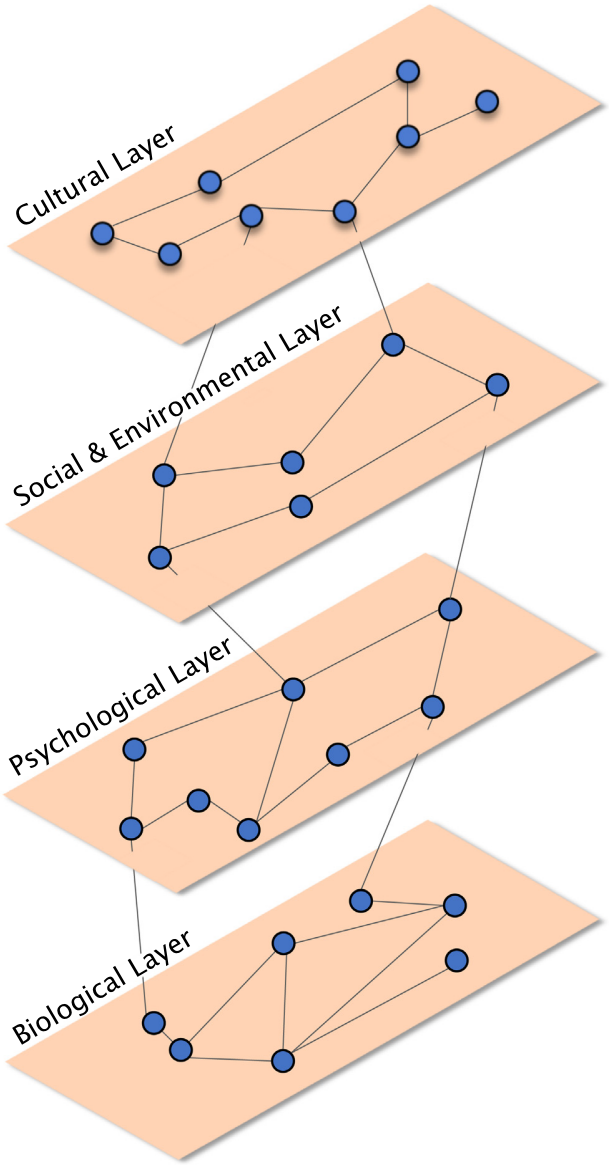


Fig. 4 Example of a Layered Networks. A series of nested networks, with a biological layer embedded within a psychological layer, embedded within a social and environmental layer, embedded with a layer or cultural and historical context. Inspired from S. Guloksuz, L.K. Pries, J. Van Os, 2017. Application of network methods for understanding mental disorders: pitfalls and promise, Psychol. Med, 74 (16), p. 3.

layers is not (yet) computationally possible (although multiplex networks are getting close; Shang, 2015), Borsboom and Cramer (2013) foresee the simultaneous analysis of social, symptom, and physiological networks as both a major challenge and a potential key merit of network models. We hope that with future improvements of network methodology and computational tools, layering networks to discover the connections between components at many different levels will be possible.

Evaluating Network Theory

Ongoing Challenges and Future Directions

As we have covered already in different sections (see "**Centrality**", "**Connectivity**", "**Comorbidity**"), network theory still lacks validation for its main tenets (Wichers et al., 2017). The network approach to psychopathology is in many ways still in its infancy. Although network theory comes with many tools stemming from graph theory (such as centrality indices) and systems science (such as early warning signals for phase transitions), these tools still need to be adapted and validated for use with psychopathology networks. Substantial work is also needed to improve the methodological robustness of network theory. There currently exists considerable variation in terms of data (pre)processing, handling of model assumption violations, model estimation techniques, and so on, all of which can affect results (Bulteel et al., 2016; de Vos et al., 2017). We currently know little about the reproducibility of network analysis results; indeed, there are very few studies that cross-validate their results by splitting their sample, and even fewer exact replications using different samples, despite the recent exponential growth in (cross-sectional) network studies (Guloksuz et al., 2017). There are a few examples of efforts to evaluate the replicability of network analyses, particularly focusing on PTSD network analyses. A systematic review and a meta-analysis concluded that the results were relatively replicable (despite large study heterogeneity), but that centrality estimates might not be that informative for the relevant networks (Birkeland et al., 2020; Isvoranu et al., 2020). Such evaluations of the replicability are needed for other domains within psychopathology network analyses, to allow a more comprehensive view of the field. Another critical challenge concerns the uncertainty regarding how to estimate adequate sample sizes for network analyses. For cross-sectional networks, post-hoc power estimations exist (Epskamp et al., 2018a), and rules of thumb for sample sizes can be borrowed from structural equation modeling (e.g., minimum 10 participants per parameter; Schreiber et al., 2006). Estimating power *a priori* to plan an adequate sample size is much more complicated and currently requires simulations based on a similar network model, which is rarely available (Epskamp and Fried, 2018). For temporal networks, even less is known about the optimal sample size and number of timepoints.

Another important consideration concerns whether the network approach should be empirically-driven or theory-driven, or both. Most network analyses currently work to uncover patterns in data, and are thus exploratory and empirically-driven. This is to be expected, considering the recency of network analyses to psychopathology (Robinaugh et al., 2019a). A number of researchers recommend moving toward confirmatory network analyses relying on formal theories, potentially using computational models of specific disorders (for further information, see Haslbeck et al., 2019; for an illustration with panic disorder, see Robinaugh et al., 2019b).

What Network Theory Brings Now

Even in its current form, however, the network perspective of psychopathology is useful. It offers a new model to understand mental disorders, with a focus on the components and their interactions instead of on one unitary syndrome. The different hypotheses stemming from a network perspective of psychopathology (e.g., the centrality hypothesis and the connectivity hypothesis) require further validation, in addition to the general methodological improvements still needed to ensure the robustness of network analyses. However, although the network perspective can be viewed as a realist model of how psychopathology truly functions (which is what its theoretical founders adopt; Kalis and Borsboom, 2020), it can also be viewed as a tool we can leverage to better understand psychopathology (van Loo and Romeijn, 2019). Following this instrumentalist interpretation, which views models as instruments to investigate the world instead of assuming they strictly represent the world, researchers can use a network perspective to better understand and predict psychopathology, without necessarily "committing to the idea that (it) provide(s) a picture of the world" (van Loo and Romeijn, 2019).

According to this instrumentalist interpretation, network models should then be used whenever they are especially suited to a research goal. For example, network models allow intuitive visualizations of how multiple symptoms interact with each other and with other components. Relatedly, network analyses can be used as a data-driven tool to investigate patterns in how symptoms cluster together and co-vary. Guloksuz et al. (2017) suggest investigating how symptoms hang together when ignoring DSM-based category diagnoses, such as by performing network analyses on broad transdiagnostic or early vulnerability data. Network models also provide intuitive ways to conceptualize and investigate comorbidity, by focusing on bridge symptoms instead of diagnostic categories (Cramer et al., 2010). Finally, with a focus on symptoms and components, network theory privileges investigating processes of change. Indeed, when researchers investigate many variables with dense time series data that allows bidirectional associations, as with temporal networks, they can investigate how symptoms change over time (Hofmann et al., 2020). Wichers et al. (2017) suggest that this is where the promise of a network perspective of psychopathology truly lies—in moving toward a dynamic view of psychopathology. Indeed, a network perspective encourages dynamic questions: Why do specific groups of people develop psychopathology? How and when do they develop or recover from psychopathology? Trying to answer these questions is essential not only for improving our understanding of psychopathology, but also for treating it.

Current and Future Clinical Applications of the Network Perspective

Even in its current formulation—still requiring theoretical validation and methodological advances—the network perspective of psychopathology already can inform clinical practice, by providing new ways to think about mental disorders. The focus on symptom interactions is generally more useful than focusing only on disorder categories, since there is often large variation of symptomatology within a diagnosis (Fried and Nesse, 2014). Many clinicians already focus on symptoms and not diagnoses when deciding on treatment options (Waszczuk et al., 2017), and the network perspective encourages research to follow this path. Research that adopts a network perspective can also yield new information on general group-level mechanisms of psychopathology, which can inform clinical treatment. It is important to note, however, that although theoretical development often requires the use of a group-level approach, these group results may not generalize to network systems as they occur within an individual, and it is these individualized networks that allow personalized clinical recommendations for a specific client (Fisher et al., 2018).

As a result, ongoing computational efforts further the growing possibilities of personalized network models. These models allow individualized insight into one person's symptom dynamics, by using intensive time series data from an individual participant to build an idiographic temporal network (for an illustration, see Fisher et al., 2017). This can allow the clinician, but also the patient, to have a personalized visual window into how their symptoms interact and feed off one another (Epskamp et al., 2018b). Personalized networks could also provide a more fine-grained approach to best identify targets for meaningful prevention and intervention (Fisher et al., 2017). With sufficient additional research, clinicians could even use insight from phase transitions and early warning signals (see "**Network Changes: Critical Transitions**" on critical transitions) to predict when a patient is about to enter a disordered state or return to a healthy one. This can allow more efficient and targeted treatment for specific individuals, while also improving general understanding about risk and resilience requisite for fine-grained clinical recommendations for a specific client.

If the network perspective and its related hypotheses (see "**Centrality**" and "**Connectivity**") were validated, then network interventions would become a possibility. The centrality and connectivity hypotheses both posit that to modify a network, turning a central node off (or on) can affect the entire network system. This opens up possibilities for very targeted interventions on a few isolated symptoms that could have large impacts. This also applies to comorbid disorders, where targeting bridge symptoms could have therapeutic effects for both/all comorbid disorders. Network interventions are the most speculative clinical application of network theory, but their specific targeting also offers an innovative way to think about and plan treatment.

We hope that future clinical developments dovetailing with the network perspective of psychopathology will follow the research branch in openly sharing data, code, methodology, and tutorials that currently characterize this field (for an example of an open textbook, see Barabási, 2016; for examples of tutorials, see Costantini et al., 2015; Epskamp and Fried, 2018; for examples of empirical studies sharing code and data, see Aalbers et al., 2018; McNally et al., 2017). For clinical applications, open materials could include open source phone applications for patients and software to automatically summarize and visualize data. This would allow clinicians to easily and inexpensively incorporate network applications within their practice, generating treatment-related insights for both them and their patients. Incorporating a network approach within clinical work meshes with the main goals of network theory: attempting to understand psychopathology in all of its complexities and iterations.

Conclusion

We demonstrated how a network perspective of psychopathology acknowledges the complexity of mental disorders by viewing them as self-sustaining systems of symptoms. A network approach to psychopathology still requires substantial development, including theoretical validation and more sophisticated statistical analyses. Nonetheless, a network perspective offers not only new theoretical avenues for research on psychopathology but also crucial translational opportunities for adapting a network perspective to inform clinical practice.

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