Problems Attract Problems: A Network Perspective on Mental Disorders

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Abstract

What is the nature of mental disorders such as major depression and panic disorder? Are mental disorders analogous to tumors, in that they exist as separate entities somewhere in people's minds? Do mental disorders *cause* symptoms such as insomnia and fatigue? Until very recently, it was exactly this sort of thinking that (implicitly) permeated many, if not all, research paradigms in clinical psychology and psychiatry. However, in recent years, a novel approach has been advocated (i.e., the *network perspective*), in which mental disorders are not conceived of as entities that have a separate existence from their respective symptoms. Instead, mental disorders are hypothesized to be networks of symptoms that directly influence one another. So, for example, from a network perspective, insomnia and fatigue are not caused by the same underlying disorder (i.e., major depression) but causally influence one another (i.e., insomnia → fatigue). A disorder, then, develops because of such direct relations between symptoms in which positive feedback mechanisms (i.e., vicious circles) are present: for example, insomnia → fatigue → feelings of guilt → insomnia. These feedback mechanisms may propel the aggravation of one's condition and make a person end up in, for example, a full-fledged depressive episode. In this contribution, we elaborate on network perspectives on the nature of mental disorders as well as their implications for our outlook on diagnosis and comorbidity.

INTRODUCTION

An undisputed and consistent fact in clinical psychology and psychiatry is that some symptoms co-occur more often with one another than with other symptoms, as such resulting in systematic and meaningful correlational patterns. Since the early twentieth century, psychiatrists such as Kraepelin and Dierendorf (1915) and Lewis (1934) have observed that, for example, depressed mood and feelings of guilt tended to co-occur more frequently with one another than, say, depressed mood and having panic attacks; and

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many others have confirmed and extended these early observations in later years. What causes these correlational patterns between symptoms?

Until very recently, the answer was: symptoms are correlated because of differences in which particular mental disorders underlie particular symptoms. Thus, depressed mood and feelings of guilt co-occur frequently because they are caused by the same underlying disorder: major depression. Likewise, depressed mood and panic attacks do not co-occur as frequently because the former is caused by major depression; and the latter by panic disorder. In that sense, mental disorders are thought to function roughly analogous to, say, a lung tumor (Borsboom & Cramer, 2013): an entity that is literally present in someone's body, and which causes a set of observable symptoms (for a lung tumor: chest pains and coughing up blood). Likewise, panic disorder is a *common cause* of its observable symptoms such as having panic attacks and worrying about having another attack (see Figure 1a; Borsboom, 2008). This *common cause* conceptualization is often echoed in the structure of the most important diagnostic tools that practitioners use to classify and diagnose mental disorders, the primary example of which is the Diagnostic and Statistical Manual (DSM) of Mental Disorders [American Psychiatric Association (APA), 1994]. In addition, many existing research methodologies are consistent with this conceptualization of mental disorders (Borsboom, 2008). For example, *latent variable models*, widely used throughout psychological/psychiatric research, are statistical models that relate a set of manifest variables (i.e., variables that can be measured such as insomnia and fatigue) to a set of latent variables (i.e., unknown or hidden common causes of manifest variables, e.g., major depression).

The recently formulated *network perspective* (see section titled Further Reading) provides an alternative explanation for the correlational patterns between psychopathology symptoms. This perspective starts out with a simple idea: Problems have the nasty habit of attracting of causing more problems. So, if one, for instance, experiences trembling hands, a racing heart, and a sense of impending doom (i.e., a panic attack), it is not surprising that one is concerned about whether such an attack might occur again: having panic attacks → concern about possible other attacks. Due to experiencing panic attacks, one might also worry about the implications of such attacks (e.g., "Am I going crazy?"): having panic attacks → worry about their implications. Finally, because of concerns and worries about previous attacks, one might change certain behaviors in order to avoid future attacks (e.g., avoiding public places): worry → behavioral changes and concern → behavioral changes. Thus, instead of positing a common cause (Figure 1a) to explain why problems such as panic attacks and worrying about these attacks are strongly associated, the network perspective views these problems as associated because they directly cause one another

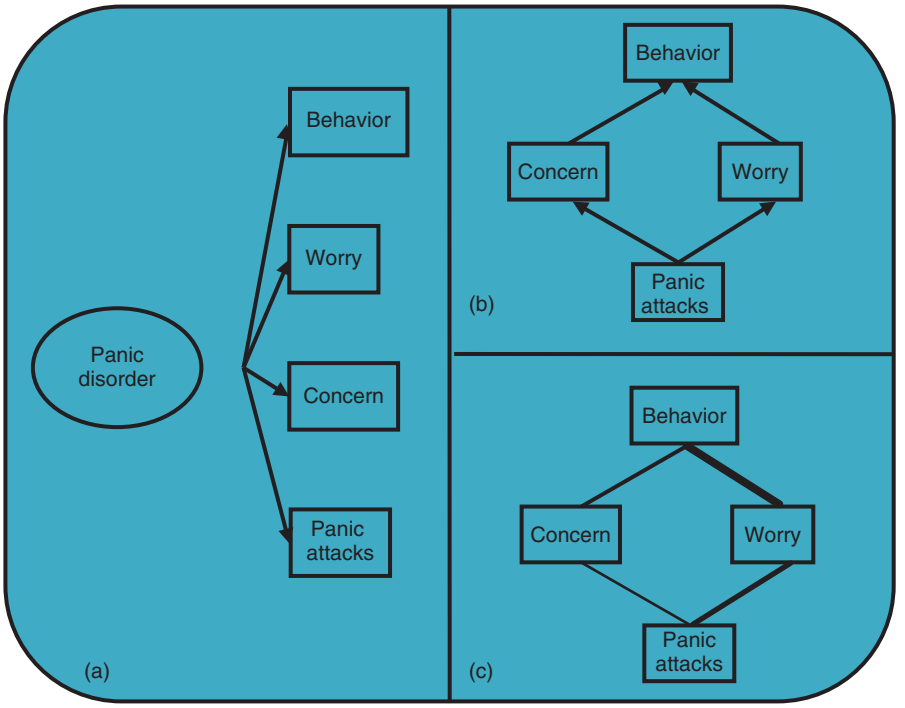

Figure 1 Panic disorder depicted as (a) a common cause, (b) an unweighted network, and (c) a weighted network. The rectangles in all figures represent the symptoms of panic disorder. (a) The circle represents the common cause or latent variable "panic disorder". (c) The thicker an edge (i.e., line) between two symptoms, the stronger the connection between these symptoms.

(Figures 1b, c). For many other psychopathology symptoms, a similar causal network between symptoms appears plausible (e.g., insomnia → fatigue in the case of major depression).

In short, a network consists of a set of entities (e.g., symptoms), which are called *nodes*, and a set of connections between these entities, which are called *edges*. Both nodes and edges are completely user-defined: that is, it is up to the constructor of the network which entities function as nodes and how the edges are defined. In the case of psychopathology, one might, as in Figure 1b, define nodes to be the symptoms of panic disorder and the edges as causal relations (this is an example of an *unweighted network* because the causal relations are not weighted by their strength). Alternatively, it is possible to define edges as representing empirical (partial) correlations between these symptoms (this would be an example of a *weighted network* because the edges are weighted by the strength of the association; see Figure 1c). When such networks are constructed, a host of techniques is available to analyze them (see Borsboom & Cramer, 2013).

It is not trivial to determine whether common cause models or network models paint the most accurate picture of mental disorders. As we outline later, the models differ with respect to their accounts of how (i) a mental disorder develops, (ii) one diagnoses the presence of a mental disorder, and (iii) the occurrence of two or more disorders within the same person (comorbidity: e.g., a person experiencing both an episode of major depression and panic attacks) should be explained. And because knowing the development of a mental disorder and its diagnosis is important in shaping the treatment of the approximately 26% of the US population who yearly suffer from a mental disorder (Kessler, Chiu, Demler, & Walters, 2005), it is vital to aim research toward elucidating the true nature of mental disorders.

FOUNDATIONAL RESEARCH

The Development of Mental Disorders

If we take the common cause reading of a latent variable (Borsboom, 2008; Reise & Waller, 2009; Figure 1a) as a blueprint for a theoretical model of mental disorders, it appears that the latent variable (i.e., the disorder) should precede its symptoms. That is, if one upholds the belief that a disorder is the common cause of its symptoms, then it follows (from the common requirement that causes should precede their effects) that the disorder should predate the development of symptoms in time. This is analogous to the case of a tumor, which is developed first and subsequently causes a certain set of symptoms.

This means that when one is interested in the pathogenesis of, say, major depression, the symptoms play no important causal role: they are merely the outcome of the development of a disorder, just as in cancer research, one is not particularly interested in the specific symptomatology of cancer patients; rather, cancer research turns on the question of how tumors are developed and treated: for example, what are the risk factors in the environment (e.g., working with asbestos) and within the individual (e.g., genetic mutations) that might increase the probability of developing a tumor? Likewise, from a latent variable model perspective, the answer to the question of how a mental disorder is developed needs to be sought at the level of that disorder/latent variable itself: what causes the disorder? Pertaining to major depression, for example, a plethora of work appears to show that major depression is associated with a number of pathophysiological correlates; for example, serotonin depletion, allelic variants of certain genes that appear to predict treatment outcome (see Cramer, 2013 for relevant literature).

The problem, however, with many of these findings is at least fourfold: (i) *specificity*: abnormalities in the serotonin reuptake function, for example,

are not only implicated in the etiology of major depression but in that of obsessive compulsive disorder, substance abuse, and anxiety disorders; (ii) *explained variance*: when combining all possible candidate genetic variants, they still explain only a very small portion of the variance in major depression; (iii) *cause or effect*: for hippocampal atrophy, for example, it is not clear whether it is a cause or effect of (repeated episodes of) major depression; and (iv) *no omnipresence*: serotonin depletion, for example, is not present in a substantial proportion of patients with major depression.

Thus, research does not seem to be consistent with the idea that disorders are consistently associated with specific abnormalities in the brains of patients, which in turn cause certain constellations of symptoms. This means that the common causes that correspond to mental disorders either do not exist or else are *very* hard to find. There are two ways in which one can respond to such a gap between theory and empirical evidence. One way, the road that has usually been taken in the past years, is that we should look harder. With more participants, better research equipment and ever more intricate ways of analyzing the data, we will eventually find the "tumor" equivalent and its associated physiological and genetic abnormalities. The other road, and the one we, and others (e.g., Kendler, Zachar, & Craver, 2011; McGrath, 2005) have taken, is to accept these findings as an indication that we may need to rethink the nature of mental disorders.

How can a person develop a mental disorder from the network perspective? The first assumption is that each individual is represented by his/her own network of symptoms. These intraindividual networks can differ markedly in terms of their *architecture*. Figure 2 presents two such fictitious networks for Alice and Bob. One architectural difference is that the symptoms in Alice's network are more strongly connected than Bob's (i.e., thicker lines between the symptoms in Alice's network compared to Bob's). This means, for example, that when both Alice and Bob are burdened by insomnia, it takes, say, only two nights with poor sleep for Alice to become fatigued while in Bob's case; only more than five consecutive nights with poor sleep will trigger fatigue. So, generally speaking, Alice has a higher probability of developing a cascade of symptoms than Bob because her symptoms are more strongly connected. This does, however, not necessarily imply that a mental *disorder* is developed. That is, most people have experienced at least a few symptoms in their lives, for example, triggered by a divorce or the death of a loved one. These symptoms might be labeled as mental *problems* but if they do not last long, there is no disorder, merely normal human reactions to life's trials and tribulations. It is when symptoms are present for prolonged periods of time (this is also a requirement for diagnosis in the DSM, a subject we return to later) that one can speak of the

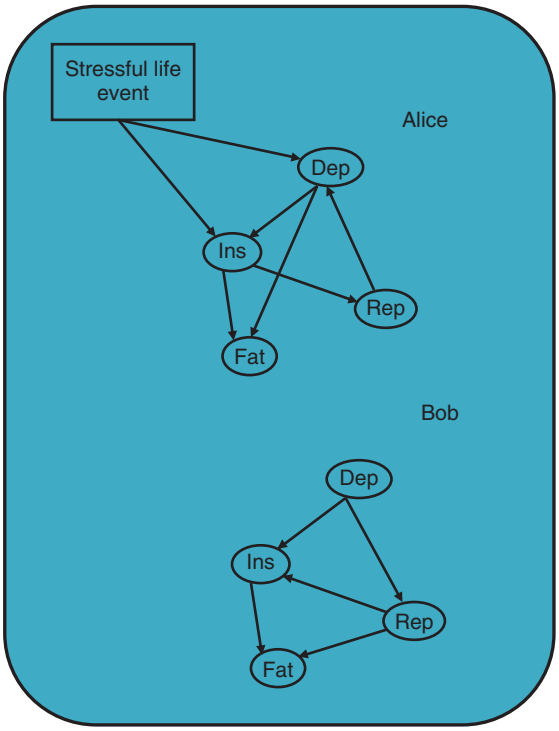

Figure 2 Two fictitious networks for Alice and Bob containing four symptoms of major depression. The thicker an edge (i.e., line) between two symptoms, the stronger the causal relation between these symptoms. Dep: depressed mood; Ins: insomnia; Rep: feelings of self-reproach; Fat: fatigue.

development of a disorder. What in the architecture of someone's network might contribute to such prolonged presence of a set of symptoms?

One likely factor is the presence of positive feedback loops. When inspecting Alice's network, one notices a chain, which at the end (i.e., feelings of self-reproach) feeds back into the start of the chain: depressed mood → insomnia → feelings of self-reproach → depressed mood. In the clinical literature, such feedback loops are better known as *vicious circles* and it is well known that such circles are crucial in the initiation and maintenance of disorders such as major depression and panic disorder (e.g., Clark, 1986; Teasdale, 1988). Research into the dynamics of other networks (or *systems*) has shown that such positive feedback loops, under certain circumstances, can result in a disordered state of the network/system (e.g., Scheffer *et al.*, 2012). Thus, the network perspective explains the development of a mental disorder not only by mechanisms that are clinically meaningful but these mechanisms also have the capacity to tip a system into a disordered state.

Diagnosing the Presence of a Mental Disorder

Until now, diagnosing the presence of a mental disorder has been largely based on DSM criteria. For example, in the case of borderline personality disorder, a person gets a diagnosis if five out of a set of nine symptoms are present. Set up in this way (with some notable exceptions, e.g., the diagnosis of major depression), the current diagnostic system treats symptoms as if they were exchangeable (see section titled "Further Reading"): any constellation of symptoms that meets the threshold (in the abovementioned example: five symptoms) suffices for getting a diagnosis. Thus Alice, who suffers from transient paranoid ideation, chronic feelings of emptiness, impulsivity, unstable interpersonal relationships, and recurrent suicidal behavior is, in terms of a borderline diagnosis, identical to Bob who suffers from efforts to avoid real/imagined abandonment, impulsivity, intense anger, identity disturbance, and affective instability (in fact, both have only one symptom in common). In the many classical epidemiological and intervention studies that have shaped our thinking about various mental disorders, it is common practice to consider all patients to be identical in terms of the fulfillment of diagnostic criteria: all get a "1" to designate the presence of a certain disorder and, generally, no distinction is made between these patients in terms of their symptomatology (with a recent exception: Rosmalen, Wenting, Roest, de Jonge, & Bos, 2012). This is all very much in accordance with latent variable models: when a, say, factor model gives rise to the data, it makes perfect sense to treat the items—in this case, the symptoms—as exchangeable. For each item (e.g., panic attack) then functions as a sort of thermometer that measures the level of the factor (e.g., panic disorder); and likewise as with temperature, as long as all thermometers are reliable (i.e., save for measurement precision), it does not matter which thermometer one uses in assessing the ambient room temperature.

In recent years, various research efforts have cast doubt on this presupposed exchangeability of symptoms. First, common sense would dictate that a patient entering a psychiatric facility with suicidal ideation is regarded to be a more serious manifestation of psychopathology than a patient with appetite problems. That is, the very nature of the symptoms themselves (thinking about killing yourself vs increased appetite) makes it hard to treat them as being exchangeable. Second, some symptoms appear to be far more predictive for developing recurrent episodes of, for example, major depression than others: People with specific residual symptoms after treatment (e.g., depressed mood, sleep/energy, and/or appetite problems) are more prone to develop another episode of major depression than people with other residual symptoms (e.g., Conradi, Ormel, & de Jonge, 2011; Pettit, Lewinsohn, & Joiner, 2006). Third, and final, different kinds of

stressful life events influence distinct sets of symptoms (Cramer, Borsboom, Aggen, & Kendler, 2012; Keller, Neale, & Kendler, 2007): for example, the death of a spouse might result in symptoms such as depressed mood and psychomotor retardation, while financial problems might trigger insomnia and self-reproach (see also Figure 2). All these findings appear to be in line with the idea that symptoms are not merely measurements of an underlying disorder, which we can subsequently count to determine whether an individual qualifies for a diagnosis. Rather, an alternative reality emerges in which symptoms are impacted by external factors such as stressful life events; and are active causal agents that trigger one another (which might culminate in a diagnosis). As such, diagnosing the presence of mental disorders by counting symptoms might be suboptimal if symptoms indeed have unique roles within the pathogenesis of mental disorders.

The network perspective accommodates the abovementioned findings naturally. For instance, it can explain how some, but not all, symptoms have the capacity to trigger recurrent episodes of psychopathology; namely, by appealing to the differential *centrality* of symptoms. In a network of symptoms, a central symptom is one that, relative to the other symptoms in the network, either (i) has more connections (in case of an unweighted network) or (ii) is more strongly connected to other symptoms in the network (in case of a weighted network; see Borsboom & Cramer, 2013). In terms of psychopathology, a more central symptom has a larger capacity to trigger the development of other symptoms. In Alice's network (Figure 2), for example, depressed mood is central because it is strongly linked to, among others, insomnia, feelings of self-reproach, and decreased appetite; and, as such, is thus able to cause these symptoms. Now, one might hypothesize that the residual symptoms that appear to trigger recurrent depressive episodes (most notably depressed mood and insomnia) are thus the central ones in the major depression network. And as we have seen in multiple datasets so far (see section titled "Further Reading"), this indeed appears to be the case.

The network perspective may also be used to improve diagnostic practices. For example, one might formulate an entirely new criterion; namely, that a set of symptoms, experienced by a person, are part of a disordered system *if and only if* they stand in a certain configuration of causal relations with respect to one another. For instance, although it is hard to deny that insomnia, fatigue, and concentration problems are unpleasant, it would be far-fetched to diagnose all new parents with a disorder, however much they suffer from these problems in response to having a newborn around. However, when the very same symptoms become part of a system that keeps itself running (e.g., when one's inability to concentrate leads one to commit errors that in turn keep one awake at night), they may be justifiably labeled as symptoms of a disorder. Reasoning in this way, the relations between symptoms rather than

their presence or absence would be used as a primary criterion in judging the presence of disorders.

Comorbidity of Mental Disorders

From a latent variable perspective, comorbidity (e.g., experiencing both an episode of major depression and generalized anxiety) is most often considered to result from one of two sources: (i) a correlation between two latent variables, for example, major depression and generalized anxiety, each of which causes its respective symptoms; or (ii) a higher order cause or "super factor" that affects these latent variables. As we have argued (see section titled "Further Reading") these accounts of comorbidity are problematic, largely because of the problems inherent in the latent variable account itself. So what, then, might explain comorbidity?

From a network perspective, comorbidity may arise through causal interactions between symptoms of multiple disorders. So, for example, a person who already has an episode of major depression might develop an additional episode of generalized anxiety through this causal chain: depressed mood → insomnia → fatigue → irritable → chronic worry, etc. Note that so-called bridge symptoms are of crucial importance in such comorbidity networks: These are the symptoms that feature in both disorders. Preliminary evidence suggested that such a model fits cross-sectional data for comorbidity between major depression and generalized anxiety disorder. Do note that these hypothetical comorbidity networks generate hypotheses that are testable in (quasi-)experiments; for example, the hypothesis that depressed mood (major depression) can cause chronic worry (generalized anxiety disorder).

CUTTING-EDGE WORK

Currently at the forefront of network research is developing models for explaining comorbidity. More specifically, recent work has shown that comorbidity is inherent in the diagnostic system DSM itself: there are many bridge symptoms, which makes progressing from one disorder to another, via these symptoms, relatively easy (Borsboom, Cramer, Schmittmann, Epskamp, & Waldorp, 2011). In addition, simulated data based on a network model with bridge symptoms for major depression and generalized anxiety disorder has shown promise in that the resulting descriptive statistics (e.g., comorbidity rate, prevalence) are in line with such statistics derived from empirical data. That is, a comorbidity network model can produce known empirical facts.

Another research project involves the relation between stressful life events and depressive symptoms. While it was known for some time that stressful life events have a differential impact on individual depressive symptoms, a recent paper showed that such events result in different correlation networks of depressive symptoms, and that these differences could not be explained by underlying differences at the level of a latent variable (i.e., measurement invariance; Cramer *et al.*, 2012; Fried, Nesse, Zivin, Guille, & Sen, 2013).

One of the hallmarks of the network approach is visualizing data to facilitate the discovery and subsequent interpretation of complex relations in data. The recently released package *qgraph*, developed for the freely available R software platform, is a free and easy-to-use tool with which one can visualize all kinds of relations in data, from correlations to factor loadings (Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012).

Another recent research project involves the development of techniques with which one can estimate and analyze networks for individual people. For example, with multilevel vector autoregression (VAR) modeling, it becomes possible to estimate network parameters based on time-series *and* let these parameters vary across individuals such that, for example, one might find that for subject 1, present insomnia is a stronger predictor for future self-reproach than for subject 4 (Bringmann *et al.*, 2013).

Also at the forefront is research that concerns the phenomenon of *early warning signals*. It is known for other complex systems with two alternative stable states (in the case of mental disorder a healthy and a disorder state), that just when the system is at the brink of tipping into another state (e.g., someone is almost developing a depressive episode), that the system displays early warning signals of that imminent transition into another state (e.g., Scheffer *et al.*, 2009). The most generic signal is that a system tends to get slower when it approaches a point of no return of tipping into another state. To translate this in psychopathological terms: If a person is on the brink of developing a depressive episode, then that person recovers more slowly than usual from events such as a nasty fallout with a family member. Recently, an analysis toolbox has come available with which one can analyze time-series data (data collected for single individuals for prolonged periods of time) in order to search for such early warning signals (Dakos *et al.*, 2012). This method holds great promise for helping patients and therapists anticipate—and maybe even prevent—transitions from health to disorder and, vice versa, to facilitate the road to mental health.

Finally, a potentially promising area of research concerns the relation between genes and psychopathology networks. While it is known that many mental disorders are at least moderately heritable, the genetic variants that are identified typically account for a very small percentage of the variance in the phenotype (e.g., major depression). That is, genes play a role in the

development of a mental disorder but we cannot seem to find these genes (i.e., the *missing heritability problem*; Cramer *et al*., 2012). The network perspective might provide an explanation for this missing heritability problem. In current genetic studies, a genetic variant is said to be associated with a particular mental disorder (e.g., major depression) if that variant predicts the sum score (i.e., the total number of symptoms someone has) on a particular inventory (e.g., depression questionnaire). As we have explicated elsewhere (see section titled "Further Reading"), this strategy does not work if a mental disorder is a network in which both the nodes as well as the edges are governed by different sets of (partially overlapping) genes. We have shown for neuroticism that, indeed, genetic variants appear to be associated with specific symptoms, not with the sum score of all the symptoms (Cramer *et al*., 2012). Prompted by the possibility that current research designs are suboptimal in case of mental disorder networks, a novel method has shown promise in detecting genes that target specific parts of a network (i.e., the Trait-based Association Test that uses Extended Simes (TATES) procedure; van der Sluis, Posthuma, & Dolan, 2013).

KEY ISSUES FOR RESEARCH GOING FORWARD

What needs to be done in order to further our understanding of mental disorders? To start, future research will need to elucidate for exactly which disorders the network approach is the best explanation and for which not. For example, while a network explanation of the pathogenesis of major depression, bipolar disorder, and panic disorder appears plausible, it seems that the origins of other disorders might not be predominantly founded upon symptom–symptom interactions. For example, in the case of development of affective symptoms after traumatic brain injury, it might be so that all symptoms are caused by the brain injury; that is, in this example, traumatic brain injury might actually be a common cause of the affective symptoms. In other disorders, it might be so that symptom–symptom interactions may be crucial in *maintaining* a pathological condition (e.g., substance use → being broke → stealing from sister to buy substance → legal problems → substance use) but that the *initiation* of repeated substance use has its roots in abnormal activity in the dopamine reward circuitry.

Another key issue for research going forward is the validation of techniques that are now in use to construct and analyze networks. We need to make sure, for example, that constructing networks in which the edges represent partial correlations and regression weights, are unaffected by, for example, sample size and variance of the nodes. Getting this right is particularly important for another key future research issue, aimed at elucidating differences in architecture between healthy people and people burdened

with a particular mental disorder: what makes networks of certain people vulnerable to end up in a psychopathological state? When, for example, comparing the network of a healthy group with the network of a patient group (and the sample sizes of these groups are unequal), it is important to verify that potential differences between these networks are due to true differences in architecture instead of being the result of differences in, say, sample size: when defining an edge to be drawn whenever a (partial) correlation is significant, the network based on the larger sample size will contain more edges than the network based on the smaller sample size; but not necessarily because the architecture of these networks truly differs but because the larger the sample size, the more correlations are significant.

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ANGÉLIQUE O. J. CRAMER SHORT BIOGRAPHY

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