Transdiagnostic Networks: Commentary on Nolen-Hoeksema and Watkins (2011)

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Abstract

Nolen-Hoeksema and Watkins (2011, this issue) propose a useful model for thinking about transdiagnostic processes involved in mental disorders. Here, we argue that their model is naturally compatible with a network account of mental disorders, in which disorders are viewed as sets of mutually reinforcing symptoms. We show that network models are typically transdiagnostic in nature, because different disorders often share symptoms. We illustrate this by constructing a network for generalized anxiety and major depression. In addition, we show that even a simple network structure naturally accounts for the phenomena of multifinality and divergent trajectories that Nolen-Hoeksema and Watkins identify as crucial in thinking about transdiagnostic phenomena.

Nolen-Hoeksema and Watkins' article (2011, this issue) is a timely call to study psychopathology at the level of processes that transcend the traditional categories of mental disorders. There is ample evidence to support this suggestion. First, approaches that have tried to identify the "essence" of common mental disorders like major depression or generalized anxiety by giving a unitary genetic, neurological, or behavioral account have failed spectacularly. Second, a wealth of evidence supports the importance of transdiagnostic processes like stress and rumination. However, we think that, in a number of ways, the theoretical framework of Nolen-Hoeksema and Watkins could be pushed a step further by moving beyond some needlessly restrictive conventions of traditional clinical research.

In our view, the current doctrine in clinical research suffers from two main problems: (a) it focuses on disorders rather than symptoms, and as such incorrectly downplays the importance of symptoms as autonomous causal entities, and (b) it often either implicitly or explicitly succumbs to the illusion of one-way causality between levels of the human system (usually genes → brain → behavior). However, when analyzed in real time, the system of genes, brains, and behavior is heavily interrelated and likely exhibits feedback both within and across levels.

Treating disorders as complex networks (Cramer, Waldorp, van der Maas, & Borsboom, 2010) solves both problems and is naturally compatible with Nolen-Hoeksema and Watkins' model. In addition, we also show that such an approach

explains many of the phenomena that concern Nolen-Hoeksema and Watkins.

The Causal Status of Disorders

Giving psychopathological conditions names like "major depressive episode" (MDE) and "generalized anxiety disorder" (GAD) makes it seductive to suppose that these disorders exist as autonomous entities that are able to receive and send out causal effects. In accordance, conventional perspectives on mental disorders typically assume that (distal or proximal) etiological factors ultimately have an impact at the level of the disorder. As an illustration, in Figure 1 of Nolen-Hoeksema and Watkins' article, proximal risk factors, depending on moderators, influence "Disorder A", "Disorder B" and "Disorder C". Disorders are then often statistically conceived of as something that a person "has" or not, more or less like the flu or a tumor.

Assuming disorders to be causal entities would make sense if there existed some level at which the heterogeneous symptom collections of current diagnoses could be traced to a single, homogeneous condition (Borsboom, 2008). For instance, despite considerable differences in symptom profiles, people

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- MD-Specific Symptoms
- Shared (Int Transdiagnostic)
- GAD-Specific Symptoms
- MD-Specific Causes
- GAD-Specific Causes
- Ext Transdiagnosic (Prox)
- Ext Transdiagnosic (Dist)

Fig. 1. A fictitious network architecture of causal entities (nodes) represented as circles and causal links between the entities represented as pointed arrows. Nodes include MDE-specific symptoms (red; e.g., depressed mood, loss of interest), GAD-specific symptoms (green; e.g., anxiety, loss of control), and symptoms shared by the disorders [Shared (Int Trandiagnostic); yellow; e.g., sleep problems]. Disorder specific external causes are colored light blue (MDE) and turquoise (GAD). External transdiagnostic proximal factors [Ext Transdiagnostic (Prox); dark blue; e.g., stress] affect both MDE- and GAD-symptoms, and mediate the effects of distal factors [Ext Transdiagnostic (Dist); purple; e.g., environmental context]. The structure of the network follows from basic assumptions explained in the text. The layout is the result of an algorithm that places nodes closer together when they are connected (Fruchterman & Reingold, 1991).

with Down's syndrome share a physical condition (namely, having all or part of an extra 21st chromosome), which reliably separates them from controls and persons with other disorders, and this condition explains the majority of symptom variance. Thus, this disorder can be "homogenized" at a deeper level than that of the symptoms and can be treated as an entity.

In contrast, MDE symptomatology ranges from concentration problems to suicidal ideation to changes in appetite; often these symptoms are themselves heterogeneous as well (e.g., depressed patients can sleep too little or too much; can have increased or decreased appetite; etc.). Now, if it turned out that these symptoms could be traced back to some empirically identifiable condition in the same vain as Down's syndrome, then it would also be sensible to treat MDE as an entity.

There is little evidence that such a homogenization is forthcoming for most disorders. For instance, although 20 years ago one could still reasonably hope that a limited number of "genes for MDE" could be identified and held responsible for a sizeable portion of the phenotypic variance, it is hard to entertain such hopes in the face of the humbling estimates of

the number of genes involved in common traits and disorders (Manolio et al., 2009). The same holds for the idea that we could reduce disorders like MDE to a simple imbalance in neurotransmitters (e.g., the serotonin hypothesis; Coppen, 1967) or to a specific psychological process (e.g., learned helplessness; Seligman, 1974). As Nolen-Hoeksema and Watkins show, the etiology of mental disorders is massively multifactorial (see also Zachar & Kendler, 2007).

Despite this fact, many researchers continue to divide the human system into "levels" or "layers" that are typically hypothesized to have intrinsic causal priority over one another (the default order being genes → brain → behavior). This idea is for instance apparent in many panic disorder theories (Fava & Morton, 2009), and it is inherent to the search for "endophenotypes" that Nolen-Hoeksema and Watkins mention. This is because endophenotypes are supposed to receive genetic effects and in turn influence higher level characteristics like cognitive function; as such, it is quite hard to even define what an endophenotype is without assuming an ordered causal scheme.

Although the default causal ordering may sometimes be justified (e.g., in parts of the etiology of Down syndrome), at other times it is not. For instance, Nolen-Hoeksema and Watkins (p. xxx) discuss a variety of neurological dysfunctions associated with clinical problems. However, it is unclear to what extent each of these are (partly) the cause of or are caused by certain (transdiagnostic) psychological disorders, or if they are purely epiphenomenal (i.e., a causally irrelevant co-occurrence). It is important to stress that we cannot justify a "reductionist default"—a default causal assumption to the effect that biology always comes first—because there are too many examples in which changes in behavior induce neurological changes in function and structure. For instance, developing chess expertise has been associated with qualitatively different neural activity patterns (Amidzic, Riehle, Fehr, Wienbruch, & Elbert, 2001), and learning new skills such as juggling has been associated with both white matter and grey matter changes (e.g. Draganski et al., 2004), both suggesting that changes in behavior can equally affect neurological properties. Similarly for hormones, although increased testosterone leads to an increase in aggressive behavior, inducing aggressive behavior also increases testosterone levels (Mazur & Booth, 1998). Even more strikingly in the context of psychopathology, childhood emotional maltreatment has been associated with a decrease in medial prefrontal cortex volume years after the incidence of abuse (van Harmelen et al., 2010). In such cases, it is more natural to consider the behavioral consequences of some trauma, such as automated thoughts or behaviors, to be a causal mediator that ultimately leads to physiological changes. It is even possible that such physiological changes may impact patterns of gene expression, thus instantiating a complete reversal of the reductionist default.

Thus, the dual ideas that (a) diagnostic categories refer to discrete causal entities and (b) that Nature has endowed psychopathology with an inherent causal order (biology first)

have dubious credentials. What then, given the complexities of psychopathology and the relative lack of success of simple biological or psychological categories in explaining these phenomena, is the best way forward?

Breaking Away From Conventional Schemes

Nolen-Hoeksema and Watkins appreciate many of the points noted above, and they suggest that transdiagnostic processes may resolve some of the problems. However, their ideas can be taken a step further when coupled with a *network perspective* (Cramer et al., 2010). In this perspective, a disorder is a system of dynamically interacting symptoms, rather than a latent entity that "underlies" or "causes" a number of symptoms. Likewise, in the network perspective, highly correlated clusters of symptoms emerge from dynamic interactions between the symptoms, rather than from underlying latent factors such as "general distress" or "positive affect", as posited in several factor models of depression and anxiety (Mineka, Watson, & Clark, 1998).

So, instead of either "having" or "not having" MDE, we conceive of MDE as a network of symptoms that are causally connected. Within a person, at any given time, these symptoms may be either "on" or "off." If Symptom A is "on," it causally influences other symptoms by increasing the likelihood of Symptom B (to which it is connected) to turn "on" as well. Although these initial steps may seem obvious (e.g., in MDE, sleeping problems increase the chance of concentration problems), examining the behavior of networks over time under certain conditions can capture many known (and problematic) features of psychopathology such as spontaneous remission and comorbidity.

Networks are transdiagnostic by nature. This is because disorders (understood as clusters of more closely connected components) typically share symptoms (or share symptoms with disorders that share symptoms with disorders that. . .). For instance, sleep loss features as a symptom in both MDE and GAD. As a component in both the MDE and the GAD network, sleep loss may be caused by feelings of self-reproach (an MDE symptom) or by chronic anxiety (a GAD symptom) and is likely to project effects back to depressed mood (an MDE symptom) and to irritability (a GAD symptom). Thus, sleep loss may act as a bridge between these two disorders, and it is expected to have transdiagnostic effects. Because these transdiagnostic effects originate in the individual itself, we may call sleep loss an *internal transdiagnostic factor*. In contrast, *external transdiagnostic factors* denote external factors, such as a death in the family. We hypothesize that symptoms that are shared between disorders in diagnostic systems, such as the *Diagnostic and Statistical Manual of Mental Disorders*, are more likely to act as bridges than are disorder-specific symptoms.

In addition, there are factors that cause a (part of the) network to become "activated" (this corresponds to the traditional idea that a person "has a disorder"). These factors are often

external events (i.e., events that are not part of the individual), although endogenous self-activation can also lead to a disordered state (e.g., feeling blue without an apparent cause). Some such factors affect only disorder-specific symptoms, whereas others affect symptoms of multiple disorders (and can therefore be described as external transdiagnostic factors). For instance, a death in the family may result in both depressed mood (a symptom of MDE) and chronic worry (a symptom of GAD). External factors affecting symptoms of multiple disorders can have either a direct (i.e., proximal) or indirect (i.e., distal) influence on symptoms. These basic assumptions allow us to construct a rough sketch of the causal architecture of the MDE–GAD symptom space as represented in Figure 1.

Simple as it is, the hypothesis that the type of architecture depicted in Figure 1 describes mental disorders has considerable explanatory power. First, the network perspective naturally explains that symptoms correlate somewhat higher within than across disorders (Nolen-Hoeksema & Watkins, p. xxx), because symptoms within disorders have more causal factors in common (namely, other disorder-specific symptoms). Second, because networks are very unlikely to be isolated, the model predicts structural comorbidity in the sense that there is no way of cutting the symptom space of mental disorders that evades significant comorbidity (Nolen-Hoeksema & Watkins, p. xxx). Third, the model explains why distinct life events have distinct symptom signatures (Keller, Neale, & Kendler, 2007): they impact the network at different points of entry (e.g., Nolen-Hoeksema & Watkins, p. xxx). Fourth, in the network model, disorders are inherently complex (they do not reflect some underlying simple variable, or variable space); thus, the network perspective naturally explains the most important discovery of the past century of clinical research, which is that there is no genetic, neurobiological, psychological, environmental, or behavioral "essence" to any of the common mental disorders. That is, rather than essentialist natural kinds, disorders are mechanistic property clusters (Kendler, Zachar, & Craver, 2010).

The network model can also accommodate multiple origins of individual differences in psychopathology. These may for instance be traced to the strength of the causal links between the variables in the network. For example, when Alice has one sleepless night she may feel tired, whereas Bob only starts to feel tired after four sleepless nights (i.e., the link between "insomnia" and "fatigue" is stronger in Alice's network compared to Bob's). Another source may lie in the plasticity of the network structure itself: for example, Alice's strong link between "insomnia" and "fatigue" is relatively easily weakened by an intervention (i.e., plastic structure), whereas in Bob's case, interventions have little effect on the link.

In our view, Nolen-Hoeksema and Watkins' model sits very well with this type of account. For instance, suppose we take the architecture in Figure 1 to characterize the average connectivity structure of a network, and view individual people (or the same individual at different time points) as variations on that theme. In such a characterization, we retain the explanation of the

"rough" correlation structure of mental disorders (e.g., Krueger, 1999) while at the same time we can explain why the same factors can pan out in qualitatively different ways for any two individuals.

For instance, the two networks in Figure 2, representing two fictitious individuals, "Mary" and "Alice," are variations on the basic MDE–GAD network, constructed by assigning different connection strengths between symptoms in a random manner. Due to the differences in the strengths of connections between symptoms for Mary and Alice, their networks differ markedly in terms of which symptoms are most likely to become activated. This indicates that the networks of different individuals will react differently to the same events, such as stress, in the sense that one type of network may primarily develop anxiety symptoms, whereas the other may primarily develop depression symptoms (divergent trajectories). At the

same time, considerable comorbidity can be expected due to (a) spreading activation through bridge symptoms (i.e., anxiety may arise as a result of depression as well as the other way around; Cramer et al., 2010), and by (b) transdiagnostic factors that influence MDE-specific as well as GAD-specific symptoms.

At the population level, empirical correlations will follow the average connectivity structure, and central nodes in that structure (i.e., factors that are involved in many symptom networks) will then become associated with many diagnoses. This explains why canonical transdiagnostic factors, like concentration problems and sleep disturbance, figure as symptoms in many disorders. Hence, the network model also accounts for multifinality. We stress that the mechanisms through which divergent trajectories and multifinality are achieved (technically, a combination of moderation and
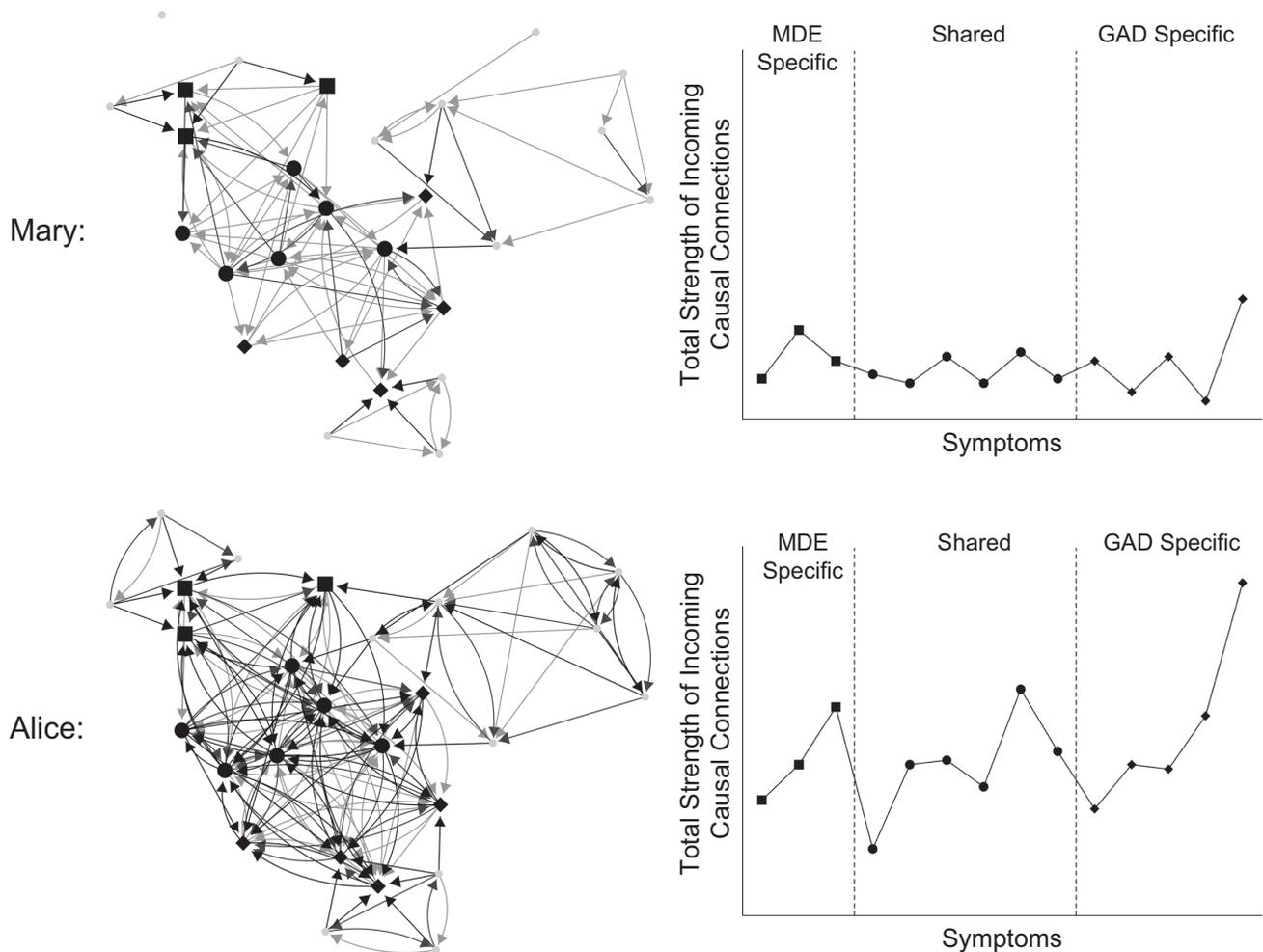

Fig. 2. Two networks of fictitious individuals, Mary and Alice, created by changing causal link parameters of Figure 1 at random. The positioning of the nodes is equal to Figure 1. Filled squares represent MDE-specific symptoms, filled circles represent Shared (Int Transdiagnostic) symptoms and filled diamonds represent GAD-specific symptoms. The graphs on the left panel represent the networks of Mary and Alice, with variable connection strengths. Stronger causal effects are depicted as darker arrows. The panels on the right are the expected symptom profiles corresponding to the two networks. These profiles represent the total strength of incoming causal connections, computed for each symptom (i.e. the sum of the number of incoming connections and their respective strengths). As can be seen, the two profiles differ markedly (divergent trajectories). In addition, these different profiles show that external factors may have different effects for different people (multifinality). However, despite these differences, the activation of distinct areas (e.g. GAD and MDE) in both networks are related due to bridge symptoms (comorbidity).

mediation) are essentially identical to those suggested by Nolen-Hoeksema and Watkins. The network model, however, has the added benefit of providing insight into the internal dynamics that govern etiology and remission.

Another important advantage of the network model is that it may nuance the distal-proximal distinction. For instance, Nolen-Hoeksema and Watkins argue that distal factors may shape an individual's beliefs, schemas, and self-images. However, such beliefs, schemas, and self-images are likely to be causally related themselves (i.e., form a network). In addition, distal risk factors are characterized to be usually, but not necessarily, independent of the individual's actions. This means that proximal risk factors could causally influence distal risk factors, which is neglected in the transdiagnostic model. Finally, the distinction between distal and proximal may not be absolute but instead context dependent. For example, being abused as a child (distal in the Nolen-Hoeksema and Watkins paper) might lead to symptom development later in life (via proximal factors) in some individuals, but in others it can lead to immediate symptom development (e.g., self-reproach and sleep problems); that is, distal factors can be proximal in certain cases (and vice versa). Such context dependencies are naturally accommodated in a network account by viewing individuals as variations on a theme, as in Figure 2.

Conclusion

The transdiagnostic model advocated by Nolen-Hoeksema and Watkins is compatible with a network model for mental disorders (Cramer et al., 2010). Here, we have outlined the form that an integrated model could take. Such a model not only accounts for multifinality and divergent trajectories, but also explains comorbidity patterns as well as the association structure of symptoms themselves. The combination of transdiagnostic models and network models opens up a rich palette of quantitative and qualitative individual differences and grounds the observations and conceptual framework in a modeling approach that may ultimately produce both a better understanding and improved interventions.

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