The glue of (ab)normal mental life: Networks of interacting thoughts, feelings and behaviors
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Chapter 5

Major depression as a complex system

Abstract
What is major depression? In this paper, contrary to a latent variable perspective on psychopathology, we argue that major depression should be characterized as a complex dynamical system in which symptoms (e.g., insomnia and fatigue) causally interact with one another: insomnia $\rightarrow$ fatigue $\rightarrow$ psychomotor retardation. Next, we hypothesize that individual people can be characterized by their own network with unique architecture and resulting dynamics. With respect to architecture, we argue that individuals vulnerable to developing major depression are those with strong connections between symptoms: e.g., for a particular person, a sleepless night has a strong influence on feeling tired the next day. Such vulnerable networks, when pushed by external forces such as stressful life events, are more likely to end up in a depressed state (i.e., “depression” attractor); whereas networks with less strong connections tend to remain in or return to a healthy state (i.e., “health” attractor). We show this with a simulation in which we model the probability of a symptom becoming ‘active’ in a person as a logistic function of the activity of its neighboring symptoms. Additionally, we show that this model explains some well-known empirical phenomena (e.g., spontaneous recovery) and accommodates both continuous and taxonomic views on major depression. Finally, we elaborate on how therapeutic strategies (e.g., cognitive behavioral therapy) can be understood within this causal systems perspective. To our knowledge, we offer the first intra-individual, symptom-based, process model with the potential to explain the empirical reality of major depression.

“Slowly, over the years, the data will accumulate in your heart and mind, a computer program for total negativity will build into your system, making life feel more and more unbearable. But you won’t even notice it coming on, thinking that it is somehow normal, something about getting older, about turning twelve or turning fifteen, and then one day you realize that your entire life is just awful, not worth living, a horror and a black blot on the white terrain of human existence. One morning you wake up afraid you are going to live.”

(Wurtzel, 2002)

Major depression (MD) imposes a heavy burden on people suffering from it. Not only are the symptoms of MD themselves debilitating, but their potential consequences such as job loss and facing stigmatization and rejection by other people can be equally detrimental to long-term physical and mental health (Greden, 2001; C. L. Hammen & Peters, 1978; Murray & Lopez, 1997; J. Wang, Fick, Adair, & Lai, 2007). Combined with the fact that major depression approximately affects 17% of the population at some point in their lives, denoting MD as one of the biggest mental health hazards of our time is hardly an overstatement (Kessler et al., 1994; Lopez, Mathers, Ezzati, Jamison, & Murray, 2006; WHO, n.d.). It should therefore not come as a surprise that vast amounts of time and money in clinical research have been allocated towards elucidating the causes of MD and effective ways to eliminate them.

One of the key questions that have to be asked first in order to investigate causes and design treatment interventions is what MD is; or, more generally, what a mental disorder is. The very notion of separate mental disorders, each associated with a specific set of symptoms, was first pioneered by Kraepelin (1923) and Lewis (1934) who, independently from each other, observed that particular symptoms tend to ‘co-exist’ with some but not all other symptoms. For example, depressed mood and feelings of worthlessness were seen together quite frequently in patients whereas depressed mood and disorganized thinking were not. Many such observations later culminated in the definition of distinct mental disorders, designating depressed mood and feelings of worthlessness as symptoms of MD and disorganized thinking as a symptom of schizophrenia. Put in statistical terms, the setup of the current classification system is based on the fact that some symptoms are more strongly correlated with one another (e.g., MD symptoms) than with others (e.g., MD symptoms with symptoms of schizophrenia; see also C. A. Hartman et al., 2001). Now, the million-dollar question is why psychopathological symptoms show these particular correlational patterns. For many decades, the short answer to this question has been that mental disorders are latent variables, common causes of their symptoms, analogous to a lung tumor that causes shortness of breath and coughing up blood (see also Borsboom & Cramer, 2013). In this chapter, we present an alternative, namely that MD should be characterized as a complex dynamical system of interacting symptoms. First, we briefly review current conceptualizations of MD as a common cause of its symptoms. Next, we outline our view of MD and show that simulated networks have characteristics that are well-known in the empirical realm, for example spontaneous recovery; and accommodate both continuous and taxonomic views on major depression. Finally, we elaborate on how therapeutic strategies (e.g., cognitive behavioral therapy) can be understood within this causal systems perspective.

MD as a common cause of its symptoms

The general idea that symptoms of a mental disorder are attributable to the same cause (i.e., the common cause view) permeates—in explicit or implicit form—the field of psy-
chiary and clinical psychology (e.g., psychosis is caused by hyperdopaminergia; Howes & Kapur, 2009) and is reflected in its mathematical formalization in psychometrics, the generic latent variable model (Borsboom et al., 2003; Cramer et al., 2010). In this model, the symptoms of MD cluster together because they share a common cause, MD: For example, the high correlation between insomnia and fatigue is hypothesized to be due to the fact that both were caused by the same underlying disorder (MD). In that sense, this model equates mental disorders such as MD to medical conditions, for example a lung tumor: in patients with such a tumor, symptoms such as chest pains, shortness of breath and coughing up blood are caused by the physical presence of the tumor. Likewise, the symptoms of Huntington’s disease are caused by an abnormal length of the Huntingtin gene resulting in a mutant Huntingtin protein (Plomin, DeFries, McClearn, & McGuffin, 2008; Walker, 2007). Additionally, in both medical conditions, there is a clear-cut distinction between people with and without the disease: all people with Huntington’s disease (or: lung cancer) have the mutant protein (or: tumor) and all people without Huntington’s disease (or: lung cancer) do not have that protein (or: tumor).

We fitted a latent variable model—that is, the statistical equivalent of the common cause view as described above—to empirical data on the nine symptoms of MD—as they are indicated in DSM-IV (APA, 1994)—assessed for the previous year from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPUD; Kendler & Prescott, 2006; Prescott et al., 2000). To be more precise, we fitted a one-factor model to this data and the results of this analysis are shown in Figure 5.1. The model fits the data nicely ($\chi^2 = 233.7, df = 27, p < .001, CFI = .998, TLI = .997, RMSEA = .029$) so one could argue: since it fits, why is the latent variable/common cause model not a good model to describe covariation among MD symptoms? One reason has to do with what happens when one fits a one-factor model to the exact same data but with the disaggregated instead of the aggregated MD symptoms. It is common practice in most, if not all, empirical papers that the latent variable model is fit onto the aggregated data in which symptoms such as insomnia and hypersomnia are collapsed (i.e., aggregated) into one symptom, sleep problems. To us, these aggregations are suboptimal since, for example, there is good reason to believe that insomnia and hypersomnia have very different functions and might even be part of distinct subtypes of MD (more on this in the next section). Nonetheless, when a common cause on MD is accurate, then one should expect that the latent variable model would hold for the disaggregated symptoms as well. In the VATSPUD data, this is clearly not the case: the one-factor model fits poorly on the disaggregated symptom data ($\chi^2 = 3366.49, df = 77, p < .001, CFI = .967, TLI = .961, RMSEA = .069$). Naturally, it is possible to tweak the model in such a way that it does fit. In this example, the model fit for the disaggregated data was good ($\chi^2 = 432.55, df = 69, p < .001, CFI = .996, TLI = .995, RMSEA = .024$) when allowing seven residual variances—based on modification indices greater than 100—to be correlated. However, although this statistically tweaked model fits disaggregated data, it is, theoretically speaking, a far cry from a common cause model: for how could one claim that a certain variable (MD in this case) is the common cause of a set of observable symptoms while at the same time allowing that, say, weight loss and decreased appetite are (cor)related?

It should be stressed that a pivotal consequence of adhering to a common cause view

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1 Other aggregated symptoms are psychomotor disturbances (agitation and retardation) and weight problems (weight loss and gain, increased and decreased appetite.

2 The following residual variances were allowed to be correlated: weight loss with weight gain, weight loss with decreased appetite, weight loss with increased appetite, weight gain with decreased appetite, weight gain with increased appetite, decreased appetite with increased appetite, insomnia with psychomotor agitation, and psychomotor retardation and fatigue.
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Figure 5.1: A one-factor model of major depression based on data from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATPSUD). The circle on top of the figure represents the latent variable “MD” whose metric was fixed such that its mean was 0 and its variance 1. The nine squares represent the nine aggregated symptoms of MD according to DSM-III-R. The grey lines (i.e., edges) from the latent variable "MD" to the squares represent the factor loadings. The vertical line in each of the squares represents the threshold above which a “yes” response is given: the further to the right the line, the higher the threshold. The dashed lines going in and out of the squares represent the residual variance. d1: depressed mood; d2: loss of interest; d3: weight problems; d4: sleep problems; d5: psychomotor problems; d6: fatigue; d7: feelings of worthlessness; d8: concentration problems; d9: thoughts of death.

is that one assumes that there are no causal relations between symptoms (i.e., no arrows between symptoms in Figure 5.1). From the common cause view, insomnia and fatigue 'co-exist' because they are caused by MD and not because they are causally related: e.g., insomnia → fatigue. In latent variable models—again, the model of choice when adhering to a common cause view—the “local independence” axiom translates this idea into statistical terms: conditioning on the latent variable (i.e., MD in Figure 5.1 renders the symptoms statistically independent (e.g., Holland & Rosenbaum, 1986; Lord, 1953; McDonald, 1981). Again, this idea makes sense for quite a number of medical diseases: involuntary jerking and lack of impulse control are likely not causally related but both caused by the mutant Huntingtin protein.

The pervasiveness of the common cause view has its roots in a mix of the philosophical traditions of disease realism, reductionism and essentialism (e.g., Haslam, 2000; Haslam & Ernst, 2002; Lilienfeld & Marino, 1999; R. Kendell & Jablensky, 2003; Thornton, 2000). Briefly, the combined views claimed mental disorders are real in the sense that it has “a real, substantial existence regardless of social norms and values, and exist independent of whether they are discovered, named, recognized, classified or diagnosed” (Freitas, 2007). As such, a mental disorder like MD is ultimately grounded in tractable biological abnormalities and a true distinction exists between people with and without MD. While we know that this is potentially true for a number of medical conditions, there is no convincing evidence for the validity of this conceptualization of MD. There is no clear-cut distinction between people with and without MD: there exists no set of biological abnormalities that are always present in people with MD vis-a-vis people without MD. Even worse, after decades of intensive research, no one has been able to even come up with a likely candidate to function as the common cause of MD (research into common causes for other clusters of psychopathological symptoms share the same fate). One could argue that we have not found those common causes yet: we will find the root causes of mental disorders like MD some day but we simply need better tools to discover them (Bollen, 2002; Borsboom, 2008b). A different take on the matter is simple:
there are no common causes to be found because they do not exist (Cramer et al., 2010; Cramer, van der Sluis, et al., 2012).

**MD as a network of interacting symptoms**

So what, then, is responsible for the established fact that symptoms of MD cluster together (i.e., are highly correlated)? Our alternative conceptualization of MD starts out with the exact opposite assumption of a common cause view concerning relations between symptoms: MD is a network of symptoms that do causally interact with one another. That is, insomnia, fatigue and concentration problems are not highly correlated because they are caused by MD but because they are causally related to each other: insomnia → fatigue → psychomotor retardation (Borsboom, 2008b; Cramer et al., 2010; Cramer, Borsboom, Aggen, & Kendler, 2012). Such direct relations make more sense than postulating a common cause: why would one need a common cause to explain why not sleeping and feeling tired are highly correlated? Likewise, if one considers the symptoms “depressed mood” and “self-reproach” it is plausible to assume a direct causal relationship: if one suffers from depressed mood long enough, at least a subset of the people experiencing this might start developing feelings of self-reproach because of these depressed feelings; and, again, this makes more sense than postulating a common cause for whose existence we have no evidence. Thus, both the common cause as well as the network perspective on psychopathology share the starting point that some symptoms are more strongly associated with one another than with others; they differ, however, in the hypothesized reason for these association patterns: a common cause, from a common cause perspective, and direct relations between these symptoms, according to the network perspective.

There are several ways to construct a network for any given set of variables. Ordinary correlations are a potential starting point but, as we have emphasized elsewhere (Cramer, van der Sluis, et al., 2012), their usefulness is limited since a high correlation need not be indicative of a direct relation between two variables. For example, it might be the case that two nodes in a network—say, self-reproach and fatigue—are highly correlated but only do so because they are both caused by a third node in the network, say, insomnia (Borsboom & Cramer, 2013). A fruitful alternative to determine which nodes are connected in a network is by exploring conditional independence relations. The package *pcalg* for R (Kalisch, Maechler, Colombo, Maathuis, & Buehlmann, 2012) can be used for the discovery of conditional independence relations from observed data. In a nutshell, the package starts out with a graph in which all nodes are connected to one another without directionality. Next, it determines conditional independence relations because these imply which nodes should be connected and which not. For example, consider the network in panel B of Figure 5.2, suppose that this network is the ‘true’ network that gave rise to a dataset: thus, in this example, both variables X and Y are caused by Z (i.e., a common cause structure). Now, such a network implies that X and Y are conditionally independent given Z (Pearl, 2000). Generally, two variables X and Y are said to be conditionally independent given a third variable Z, denoted as X ⊥ Y|Z, iff Pr(Y|X,Z) = Pr(Y|Z). That is, X and Y are conditionally independent if the probability of Y given X and Z is the same as the probability of Y given Z alone: values of X thus give no additional information about the probability of Y occurring. And because X does not contribute information, beyond the information contributed by Z, to the probability of Y, the program removes the edge between X and Y. *pcalg* searches the dataset for all such relations (for all possible combinations of nodes in the network including all interactions) to delete edges from the completely connected network. In the next step, it infers the directionality of the edges by, for example, exploiting the special
case of the collider (see panel C of 5.2). A collider, $Z$ in panel C of Figure 5.2, is a node that is the outcome of two other variables, $X$ and $Y$. In this particular case, $X$ and $Y$ are conditionally dependent given $Z$. Once search algorithms like $pcalg$ find such colliders, the edges are oriented accordingly. On a cautionary note, a limitation of these and similar search algorithms is that a set of conditional independencies can be consistent with multiple graphs (these graphs are said to be Markov equivalent): for example, the networks in panel A (i.e., causal chain) and B (i.e., common cause) of Figure 5.2 imply the same, single, conditional independency: $X \perp Y \mid Z$. This means that when using such search procedures, it would be premature to claim the discovery of the network that gave rise to the conditional independence relations between a given set of variables. A network for a particular sample discovered through causal discovery algorithms such as $pcalg$ would need independent verification in unrelated samples; and/or, additional variables could be added as extra nodes in the network in order to facilitate the process of determining directionality of the edges.

Figure 5.2: An illustration of the three most important causal relations that can be discovered through tracking conditional independence relations. Panel A shows a chain structure: $Z$ functions as a mediator between $X$ and $Y$. Panel B shows a common cause structure: $Z$ acts as the common cause of both $X$ and $Y$. Panel C shows a collider structure: $Z$ is a common effect of both $X$ and $Y$.

Figure 5.3 presents such a graph derived from $pcalg$ for the VATSPUD data. In this figure, each symptom is represented as a node while each line (i.e., edge) between two nodes implies that these nodes are conditionally dependent, given all combinations of other nodes in the network. We have omitted arrows in this figure so all edges are interpreted as bidirectional connections. The positioning of the nodes is such that nodes with many connections with other nodes are placed towards the middle of the graph; while nodes with relatively few connections with other nodes are placed towards the periphery of the graph. The first thing that stands out when inspecting Figure 5.3 is that a couple of symptoms appear to be isolated from the remainder of the network: most noteworthy in this respect are weight loss ($wlos$), weight gain ($wgai$), increased appetite ($iapp$) and hypersomnia ($hsom$). Pertaining to the latter three, the fact that these appear to be somewhat isolated from the other symptoms of MD might not come as a surprise since the distinction between MD with typical (e.g., weight loss, decreased appetite, insomnia) versus atypical (e.g., weight gain, increased appetite, hypersomnia) symptoms was first observed and articulated into theory many decades ago (e.g., D. F. Klein & Davis, 1969) and is currently recognized in the most recent version of the DSM (i.e., DSM-IV; APA, 1994). Second, some symptoms are clearly more central than others: these nodes have relatively many connections with other nodes in the network. Consistent with the diagnostic importance that DSM-IV assigns to depressed mood and loss of interest—either one of these symptoms must be present for a diagnosis of MD—these symptoms ($depr$ and $inte$) rank among the most central symptoms in the MD network. On a final note, many of the connections in Figure 5.3 make intuitive sense: for example, the connec-
tion between insomnia (isom) and fatigue (fati); the connection between fatigue (fati) and concentration problems (conc); and the connection between feelings of worthlessness (wort) and thoughts of death (deat).

Figure 5.3: A network model of major depression derived from conditional independence relations and based on the VATSPUD data. Each node in the figure represents one of the 14 disaggregated symptoms of MD according to DSM-III-R. A line (i.e., edge) between any two nodes means that they are conditionally dependent, given all possible subsets of other nodes in the network. The absence of an edge indicates conditional independence. depr: depressed mood; inte: loss of interest; wlos: weight loss; wgai: weight gain; dapp: decreased appetite; iapp: increased appetite; isom: insomnia; hsom: hypersomnia; pret: psychomotor retardation; pagi: psychomotor agitation; faï: fatigue; wort: feelings of worthlessness; conc: concentration problems; deat: thoughts of death.

Recent (circumstantial) evidence appears to be in favor of the network model for MD (Cramer, Borsboom, et al., 2012). For example, the death of a spouse triggers depressed mood (depr) and loss of interest (inte) while health problems trigger insomnia (isom) and psychomotor retardation (pret) in Figure 5.4 (i.e., the solid arrows); and this phenomenon cannot be explained by underlying differences in the common cause (i.e., the dashed arrows in Figure 5.4): for example, the fact that the death of a spouse triggers more depressed mood and loss of interest compared to health problems, cannot be explained by the death of a spouse causing a higher score on the common cause/latent variable “MD” compared to health problems. This result points to the unique role that MD symptoms appear to play in the pathogenesis of MD: each receives, potentially unique, input from external variables such as stressful life events. And this unique role of individual symptoms is hard, if not impossible, to explain from a latent variable or common cause perspective where, by the very implication of positing a common cause, all external influences (such as stressful life events) should run via the common cause.
Figure 5.4: Two potential ways in which stressful life events (i.e., the death of a spouse and health problems) can impact major depression. The circle with “MD” represents the latent variable “major depression” while the rectangular boxes represent the 14 disaggregated symptoms of MD. First, a stressful life event can influence the latent variable MD directly and not the symptoms (i.e., dashed lines from Death spouse and Health problems to MD). This setup is consistent with a latent variable perspective. Second, a stressful life event can influence the symptoms directly and not the latent variable (i.e., solid lines from Death spouse and Health problems to depr, inte, isom and pret). This setup is consistent with a network perspective.

depr: depressed mood; inte: loss of interest; wlos: weight loss; wgai: weight gain; dapp: decreased appetite; iapp: increased appetite; isom: insomnia; hsom: hypersomnia; pret: psychomotor retardation; pagi: psychomotor agitation; fati: fatigue; wort: feelings of worthlessness; conc: concentration problems; deat: thoughts of death.

The intra-individual network model of MD

The network in Figure 5.3 is based on inter-individual data and as such, without additional testing of the mapping between what happens at the inter-individual level and what happens within an individual, could not serve as an intra-individual network model of MD. How, then, could we model what happens at the intra-individual level? Let us start with explication how one could conceive such a model. First, we assume that symptoms can be ‘on’ (1) or ‘off’ (0) and can influence one another in time if they are connected in the graph based on conditional independencies derived from the VATSPUD data (Figure 5.3). Symptoms that are connected in this graph are called neighbors of one another. In Figure 5.3 for example, hypersomnia has only two neighbors (increased appetite and fatigue) and only these neighbors can influence hypersomnia. Likewise, psychomotor retardation has five neighbors (loss of interest, increased appetite, fatigue, feelings of worthlessness and concentration problems). The state (0: ‘on’ or 1: ‘off’) of a symptom $i$ at time $t$ is denoted $X_{ti}$. The connection between symptom $i$ and $j$ is denoted $W_{ij}$ and can be considered as a binary variable (connection is either present (1) or absent (0) as in the connections in Figure 5.3) or a continuous variable (for example ranging from -1 to 1 reflecting partial correlations). Furthermore, there is no autocatalysis: the weights $W_{ii}$—that is, a connection (self-loop) between a symptom and itself—are set to 0. The matrix $W$ contains all weights of the connections between $J = 14$ symptoms.

Next, we assume that the probability of a symptom to turn ‘on’ (i.e., becoming present/active in a ‘person’) depends monotonically on the activation of its neighbors: the more neighbors of symptom $i$ are ‘on’ at a given point in time, the higher the probability that symptom $i$, at a later point in time, becomes present itself. The total activation function of symptom $i$ at time $t$ is:

$$A_{ti} = \sum_{j=1}^{J} W_{ij} X_{tj}$$

Thus, when connections between symptoms are stronger and more symptoms are
turned ‘on’, A becomes increasingly large. As a next step, the probability of a symptom $i$ becoming active at time $t + 1$ depends on $A_t^i$ and is expressed as follows:

$$P(X_{t+1}^i = 1) = \frac{1}{1 + e^{a_i(b_i - A_t^i)}}$$  \hspace{1cm} (5.2)

Note the similarity of this probability function with the probability function for an item in a Rasch model (Rasch, 1960) and the conditional probability of a variable given its neighbors in the classical Ising model (Ravikumar, Wainwright, & Lafferty, 2010) (see Appendix F for more details on the exact correspondence of our model with the Rasch model and the Ising model). In the current function, the parameter $b_i$ gives the threshold of symptom $i$. Symptoms with higher thresholds require more activation, while symptoms with lower thresholds are easily activated. A special case arises when $A$ is equal to $b_i$, that is, when the amount of activation of the neighbors of symptom $i$ is exactly equal to the threshold of symptom $i$. In that case, the probability of symptom $i$ becoming active is exactly 1/2. Given known prevalence differences in MD symptomatology—for example: sleeping problems are more prevalent than thinking of suicide—threshold differences between symptoms appear to be a reasonable modeling assumption. The parameter $a_i$ is a symptom-specific parameter that controls the steepness of the probability function: for higher levels of $a_i$, a given change in $A_t^i$ results in a steeper change in the probability of symptom $i$ becoming active. Together, formulas 5.3 and 5.2 control the dynamic behavior of the system. We implemented the model in the freely available program NetLogo (van Borkulo, Borsboom, Nivard, & Cramer, 2011).

The above formulas describe the dynamic behavior of one network over time. Suppose we would simulate many of these networks to represent individuals, how might these networks differ in their architecture? We hypothesize two things: First, individuals’ networks differ in terms of the connections between symptoms; that is, individuals might have a different $W_{ij}$ matrix. In substantive terms for binary weights, this might mean, for example, that insomnia has no neighbors in Alice’s network (i.e., for Alice, poor quality of sleep does not influence other symptoms in her network); while in Bob’s network, insomnia has eight neighbors (i.e., in Bob’s case, poor quality of sleep influences many other symptoms in his network). When the connections are considered to be continuous, then a strong connection between, say, insomnia and fatigue in someone’s network of MD means that poor sleep one day has a substantial impact on feeling fatigued the next day: this person likely will feel tired after a night with poor sleep. On the other hand, a weak connection between insomnia and fatigue means that poor sleep one day has only a limited impact on feeling fatigued the next day: this person likely will not feel tired after a night with poor sleep. Second, we hypothesize that someone who is vulnerable to develop an episode of MD has a network in which the MD symptoms are generally strongly connected: according to formulas 5.3 and 5.2, if one symptom is developed in networks with high connectivity, then the probability of other symptoms quickly becoming activated as well is high, due to (1) the presence of relatively many connections (in case of $W_{ij}$ containing binary weights) or (2) the overall strong connections (in case of $W_{ij}$ containing continuous weights) in that network. The worst case scenario, in terms of vulnerability, is the combination of strong connections between symptoms and relatively low thresholds: in that particular case, not much activation of neighboring symptoms is needed to exceed the threshold of a symptom and, as such, activate it. On the other hand, relatively high thresholds might ‘protect’ a person from harm because in that case, despite strong connections, al lot of neighboring symptoms need to be activated in order to exceed the threshold. Resilience can be thought of as a network in which the symptoms

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3 The simulation tool can be downloaded at http://ccl.northwestern.edu/netlogo/models/community/Symptom%20Spread%20Model
are weakly connected: the development of one symptom is not likely to set off a cascade of symptom development culminating in an episode of MD; because the relations are not strong (or not omnipresent in the case of binary weights), thereby having a relatively small impact on the probability of symptom development.

To incorporate the possibility of different weight matrices and study the potential impact on the behavior of the network, we adapted the formula in 5.2 to include a connectivity parameter \( c \), a number that is identical for all symptoms with which matrix \( W_{ij} \) is multiplied: the higher \( c \), the more strongly the symptoms are connected:

\[
A^t_i = \sum_{j=1}^{J} cW_{ij}X^t_j
\]  

(5.3)

For our simulations, \( c \) took on three values to create networks with low (lowest value of \( c \)), medium and high connectivity (highest value of \( c \)). At all time points during simulations, we tracked the global mood state, \( M \), of these networks by computing the total number of activated symptoms at these time points. We simulated 10000 time points with this basic intra-individual MD model for each of the three values of \( c \) to investigate whether, as we predict, stronger connectivity results in higher levels of \( M \).

The \( a_i \) and \( b_i \) parameters for the probability functions of the 14 symptoms were derived from fitting a logistic regression to the VATSPUD data, in which each symptom was regressed on the total score of its neighbors in the network model as it is presented in Figure 5.3. Detailed results as well as R scripts are available at www.aojcramer.com. The most important result is that, as we predicted, the higher the connectivity of the network, the higher the mood state \( M \) averaged over the 10000 simulations. That is, more strongly connected networks are more vulnerable in that they become “depressed” more easily.

Another important result has to do with the weakly connected network in particular. It is a well-known, but relatively understudied, phenomenon that quite some individuals who suffer from an episode of MD recover independently of treatment. Estimates of this spontaneous recovery range somewhere between 23% and 98% (e.g., see Krøgsboll, Hrøbjartsson, & Gøtzsche, 2009; Kendler, Walters, & Kessler, 1997; Whiteford et al., 2012) depending on the exact time frame within which people with MD are observed and on whether these people have received treatment: for example, the spontaneous recovery rate is around 23% for untreated individuals within three months while it is around 90% for a community sample within a year combining both treated and untreated individuals. In treatment studies, these people are, when identified, omitted from the statistical analyses and preferably, the baseline period before the start of a treatment intervention is increased such that as little spontaneous recovery as possible ‘contaminates’ the results. While a sensible requirement when the aim is to study the effects of a treatment intervention, it has resulted in very limited knowledge about the naturalistic course of major depression (see: Posternak et al., 2006). As a result, there are no solid theories about how spontaneous recovery might come about. To our knowledge, the results of this basic simulation study are the first to hint at a possible mechanism through which spontaneous recovery might occur. See Figure 5.5 in which the mood state \( M \) (y-axis)

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\footnote{Parameter estimates are available at www.aojcramer.com. Please note that the intercept \((b_i)\) and slope parameters \((c_i)\) derived from logistic regression for each symptom on the total score of its neighbors \((S_i)\) (i.e., \( P(X_{i}+1 = 1) = \frac{e^{b_i + c_i S_i}}{1 + e^{b_i + c_i S_i}} \)); do not have a one-to-one mapping with our \( a_i \) and \( b_i \) parameters in \( P(X_{i}+1 = 1) = \frac{1}{1 + e^{a_i(b_i - A_i)}} \). Such a mapping can be achieved by setting our \( a_i \) parameter to be equal to the \( c_i \) parameter of the logistic regression; and our \( b_i \) parameter to be equal to \( -\frac{b_i}{c_i} \).}
for a weakly connected network is shown for the first 2000 time points. The figure clearly shows spontaneous recovery: that is, there are points (e.g., at time points 50 and 600) where many symptoms are activated and, without any change to its parameters, the system recovers spontaneously to a state in which no symptoms are activated.

Figure 5.5: The mood state of the MD system over time. The x-axis represents the first 1000 time points of the basic simulation with the MD network model while the y-axis depicts the mood state; that is, the total number of activated symptoms at a given time point. The figure shows the presence of spontaneous recovery: there are distinct peaks in the mood state, which, without intervening in the parameters of the system, spontaneously return to lower mood states.

Vulnerability to develop MD: a catastrophe?

Our current knowledge of how stress (in interaction with vulnerability) can cause episodes of MD is based on inter-individual differences: for example, in Chapter 4, inferences about the impact of stress on symptoms of MD were made by comparing groups of individuals. As such, we have no clear idea of what happens inside an individual person when put under stress, which might or might not result in an episode of MD. Therefore, in order to investigate the impact of stress on intra-individual networks, we extend our basic network model of MD, explicated in the previous section, with a stress parameter $S_i^t$, a number for each symptom $i$ that is added to the activation of the neighbors of $i$: the higher $S_i^t$, the more stress, the higher the total activation function, and thus the higher the probability that symptom $i$ will become active. This results in the following modified activation function:

$$A_i^t = \sum_{j=1}^{J} W_{ij} X_j^t + S_i^t$$  \hspace{1cm} (5.4)
Thus, in our model, stress $S_i$ triggers the development of one or more symptoms of MD. It then depends on the strength of the connections between the MD symptoms ($W$) whether the symptoms that were developed due to the stressor cause the development of other symptoms. If someone is vulnerable (i.e., symptoms are strongly connected), a mild stressor triggering the development of one symptom could be enough to trigger a cascade of symptom development eventually culminating in a full-blown episode of MD (i.e., large $M$). In a resilient person/network, a relatively large stressor might trigger the development of one or a few symptoms, but these symptoms will not likely cause the development of other symptoms. Consider an analogy with a bowl containing a ball (see also Figure 5.6): the ball is the MD network and the lowest point of the bowl is one of two possible mood states (alternatively called: attractors or basins of attraction), a healthy euthymic state and a depressed state. Now, when someone is resilient (i.e., at low risk to develop MD), stressors are capable of pushing the ball out of the healthy attractor but when the stressor diminishes, the ball quickly rolls back towards that healthy attractor. That is, in a resilient person, there is a quick homeostatic return to the prior mood state. Box A of Figure 5.7 illustrates this: larger stressors only slightly affect mood along the equilibrium attractor curve.

We hypothesize that the MD symptom networks of people who are vulnerable to develop MD (i.e., strongly connected networks) behave like what is known in the complex systems literature as a cusp catastrophe model (Ehlers, 1995; Flay, 1978; Goldbeter, 2011; M. T. Hubert, Braun, & Krieg, 1999; Thom, 1975; Zeeman, 1977). The catastrophe model is a mathematical model that can explain why small changes in some parameter (in our case: small increment in the stress parameter $S_i$) can, under certain circumstances, result in catastrophic changes in the state of a system (in our case: a catastrophic shift from a healthy to a depressed state, and vice versa). In the case of someone who is vulnerable to develop MD, even a small perturbation like a particularly bad day at work has the potential to push the ball outside the healthy attractor, causing it to roll towards another attractor, namely that of the depressed state (see also Figure 5.6). If this depressed basin of attraction is large and deep, the network of MD symptoms may become solidly locked in the depressed state. But under what circumstances can such a catastrophic shift from health to MD happen?

Box C of Figure 5.7 illustrates three features of a cusp catastrophe model that, combined, can bring about catastrophic semi-permanent changes in response to small perturbations. First, the equilibrium curves are folded backwards with multiple equilibria for a given stressor as a result: e.g., a divorce might result in the MD network ending in the healthy or depressed attractor. Second, the equilibrium attractor curve contains two tipping points that represent the border between the basins of attraction of the two alternative stable states on the upper and lower branches (Scheffer et al., 2009). Near such tipping points the equilibrium is unstable (dashed middle sections in Box C of Figure 5.7), meaning that modest disturbances (e.g., a small argument with a spouse over which restaurant to go to) may already move the network away from the healthy attractor instead of returning to it; and may even result in a large catastrophic affective shift to the depressed state. Third, the two alternative stable states of the MD are stable, implying that once the MD network has gone through a catastrophic affective shift, it tends to remain in that new affective state until the external input (i.e., stress) is changed back to a much lower level than was needed to trigger the episode of MD; a phenomenon known as hysteresis (see also Box C of Figure 5.7). That is, this model predicts that Bob, who developed an episode of MD in response to severe marital problems, will not recover automatically when, for some reason, the current marital problems are solved: more is needed, for example additional treatment, to trigger Bob’s recovery.
Figure 5.6: Three-dimensional landscape model for major depression (MD). Stable affective states are represented as curvatures (i.e., wells), in a two-dimensional surface. The model contains two tipping points, represented by blue dots, resulting in two equilibria or stable states (solid green lines in the two wells) that exist for a given stressor. The green dotted line marks the unstable state, as the equilibrium curve is folded backwards. The balls represent the MD network. Far from the bifurcation point (1), resilience is large because the basin of attraction in the deep well of the healthy state is larger with a high rate of recovery from perturbations. This state is typical for a MD network with weakly connected symptoms. Under gradual influence of stress, the well becomes shallower and the basin of attraction shrinks (ball progressing along the red arrow from 1 to 2). More symptoms become activated (marked by red nodes). The basin finally vanishes at a critical threshold (i.e., bifurcation points or tipping points), causing the ball to abruptly roll towards the depressed state attractor (progressing along the red arrow from 2 to 3).

The simulation

For the actual simulation that tested our hypotheses regarding the behavior of weakly, medium, and strongly connected MD networks in response to stress, we—similar to the basic MD network model—simulated 10000 time points for each of the three connectivity $c$ values. For these three types of networks, we observed the impact of variation in the stress parameter: over the course of the 10000 time points $S_t$ was repeatedly gradually increased as well as gradually decreased from -15 to 15 with small steps of 0.01 (for details of the simulation see www.aojrcramer.com). The impact of the stress parameter on the behavior of the network was quantified by computing the average global mood state $M$: that is, since all stress parameter values were used multiple times during the simulation, we averaged mood states within 0.20 ranges of the stress parameter values.

Figure 5.8 shows the main results of the simulation: the $x$-axis represents stress, $S_t$, while the $y$-axis represents the global mood state $M$. The red line represents the mean number of activated symptoms (for stress parameter values within 0.20 ranges) when stress was increasing and the blue line represents the mean number of activated
Figure 5.7: Diagrams of potential (critical) transitions in affective states in a cusp catastrophe model. The two control variables are connectivity of the MD network and stress. The equilibrium state of the mood system can respond in different ways to stress. Red arrows in the plots indicate the direction in which the system moves under the influence of stress. Box A: In resilient people, severe stress results in relatively modest changes in the affective state, the system quickly returns to its prior state. A resilient person is not immune to stress, but is able to re-establish equilibrium following stressful experiences. Box B: In more vulnerable people, relatively small stressors may induce a larger drop in the affective state. Small stressors thus can cause relatively large changes in the absence of true bifurcations, provided that the system is very sensitive along a certain range of stressors. Box C: The equilibrium is folded backwards in a model for some of the more severe forms of depressive disorders, resulting in two tipping points (i.e., critical thresholds or bifurcation points; marked by blue dots) and two alternative stable states for a certain set of values of the stress parameter. This represents the cusp catastrophe model. When the MD system is near a tipping point (i.e., critical threshold), a small disturbance may result in a catastrophic affective shift towards an episode of MD as the system jumps to the far-away attracting lower branch.

Symptoms (for stress parameter values within 0.20 ranges) when stress was decreasing. As a general result, differences in the strength of connections between MD symptoms resulted in markedly different responses to external activation by stress. MD networks with low connectivity proved resilient (left panel of Figure 5.8): stress increments led to a higher number of developed symptoms in a smooth continuous fashion, and stress reduction resulted in a smooth continuous decline of symptom activation. The dynamics were very different for the networks with medium and strong connectivity, which proved vulnerable (middle and right panel of Figure 5.8, respectively). Here, the shift between healthy and depressed states was of a non-linear character as two tipping points appeared: a small increase in stress could lead to a disproportional reaction, resulting in a depressed state. Additionally, these vulnerable networks needed a significant decrease in stress to move the network back to a healthy state. The middle (medium connectivity) and right (high connectivity) panel of Figure 5.8 also clearly show that during the transition from the healthy to the depressed state or vice versa, a ‘forbidden’ zone (from 1 to 5
activated symptoms) was crossed that does not seem to function as a stable affective state. Moreover, hysteresis, as we anticipated earlier, was evident in the networks with strong connectivity: in order to make these networks return to a healthy state, the stress level needed to be reduced to a level far below the level of the initial external activation by stress. Thus, a cusp catastrophe was present for such networks. Thus, in sum, the results of this simulation as visualized in Figure 5.8 highly resemble the hypothesized behavior of MD networks as visualized in Figure 5.7. In the remainder of this section, we describe some of these results, and, if applicable, their connection with the empirical reality of MD, in greater detail.

![Figure 5.8: The mood state of the MD system in response to stress. The x-axis represents stress while the y-axis depicts the average mood state: that is, the total number of activated symptoms averaged over every 0.20 range of the stress parameter value). The red line depicts the situation where stress is increasing whereas the blue line depicts the situation where stress is decreasing. The three graphs represent, from left to right, the simulation results for networks with low, medium, and high connectivity, respectively.](image)

### Hysteresis

As we hypothesized, the results of the simulation of a network with high connectivity showed clear hysteresis: the amount of stress reduction needed to get the system into healthier mood states (i.e., only a few symptoms present) exceeds the amount of stress that tipped the system into depressive mood states in the first place. We do not know of other (simulation) studies that showed this phenomenon to be present in ‘individuals’ vulnerable to developing episodes of MD. It does seem to resonate with clinical observations concerning the non-linear course of affective shifts between healthy and depressed states that is frequently encountered in the empirical literature: it takes relatively little time to induce an episode of MD by mild stress, but it takes more time to recover from such an episode because more is needed for recovery, besides removing the stressor that initially triggered the development of the episode (e.g., Penninx et al., 2011).

One could argue, since we have used one specific setup of the simulation with specific choices for (empirically derived) parameters, that the hysteresis effect is an effect of this specific setup; and that, as such, the observed hysteresis is not a robust phenomenon that can be consistently associated with high connectivity networks. In order to check the robustness of the hysteresis effect, we repeated the simulations in which we systematically varied five parameters: (1) weights $W_{ij}$: either discrete (as in our original setup) or continuous (with uniformly distributed values between 0 and 1), (2) connectivity pa-
rameter $c$ ranging from 1 to 3, (3) number of nodes $J$ in the network: 5, 10, 15 or 20, (4) the $b_i$ parameter which was randomly sampled from a normal distribution in three configurations: $\mu = 1$ and $\sigma = 0.25$, $\mu = 1.50$ and $\sigma = 0.50$ or $\mu = 2$ and $\sigma = 0.75$ and (5) the $a_i$ parameter which was randomly sampled from a normal distribution in three configurations: $\mu = 1$ and $\sigma = 0.25$, $\mu = 1.50$ and $\sigma = 0.50$ or $\mu = 2$ and $\sigma = 0.75$. Each simulation consisted of 10000 time points and each combination of parameter values was simulated 20 times. For each simulation we computed a hysteresis effect $H$: for both increasing and decreasing stress (the same red and blue lines, respectively, as in Figure 5.8), we determined the point at which the mood state (i.e., symptom sum score) was closest to the midpoint $J/2$ (i.e., half of symptoms activated). Subsequently, the hysteresis effect was computed by subtracting the point at which the increasing stress line was closest to the midpoint from the point at which the decreasing stress line was closest to that same midpoint. A value of 0 thus indicates no hysteresis (point at which symptom sum score is closest to the midpoint is equal for both increasing as well as decreasing stress) while increasing positive values $H$ indicate a larger hysteresis effect: the larger $H$, the more stress reduction is needed to reduce the sum score to roughly half the symptoms when stress is decreasing; compared to the amount of stress that results in the activation of roughly half of the symptoms when stress is increasing. For every 20 simulations with the same parameter values, we computed the average hysteresis effect on which subsequent analyses were based.

Figure 5.9 shows the average hysteresis effect for the five parameters whose values we varied systematically. First, with linear models, we estimated the impact of each parameter on the hysteresis effect. Most importantly, the connectivity of the network significantly impacted the amount of hysteresis (as we found in our main simulation; estimate: 3.75, $t = 11.02, p < .001$): the more strongly connected the network, the larger the hysteresis effect. Additionally, except for the $b$ parameter, all other parameters influenced the hysteresis effect significantly: continuous weights result in a more pronounced hysteresis effect compared to discrete weights (estimate: 1.93, $t = 3.47, p < .001$); the more nodes in the network, the stronger the hysteresis effect (estimate: 0.70, $t = 9.94, p < .001$); and the higher the mean of $a$, the stronger the hysteresis effect (estimate: 4.10, $t = 6.02, p < .001$). Finally, two interaction effects (computed with all variables being centered around their respective means) were significant as well: the effect of connectivity on the hysteresis effect was even stronger for an increasing (1) number of nodes in the network (estimate: 0.40, $t = 6.57, p < .001$) and (2) mean of the $a$ parameter (estimate: 2.59, $t = 3.09, p < .001$). As such, we conclude that the hysteresis effect is robust in that increasing connectivity of a network results in more hysteresis; and that this effect is more pronounced for networks with more nodes and a probability function with a higher average $a$ parameter.

**Taxa versus continua**

The question whether psychopathological conditions are instances of taxa (i.e., distinct categories, natural kinds) or continua (i.e., a continuous dimension with psychopathology located at an extreme of that continuum) is an old one and one without a definitive answer (e.g., Flett, Vredenburg, & Krames, 1997; R. E. Kendell, 1975; R. Kendell & Jableanksy, 2003; Haslam, Holland, & Kuppens, 2012; Meehl, 1992; Waller & Meehl, 1998; Widiger & Samuel, 2005). There is evidence for both views although the last few years, more evidence seems to point into the direction of psychopathological conditions being continua (e.g., Haslam et al., 2012), which poses a challenge for diagnostic schemes, such as the DSM that offer categorical perspectives on psychiatric diagnosis. Pertaining to major depression specifically, the results are inconclusive: for example, Baldwin et al. (Baldwin
& Shean, 2006) report evidence, based on taxometric procedures, that total scores on the Center for Epidemiological Studies Depression scale (CES-D) were best represented as a continuum; while Ruscio et al. (Ruscio, Zimmerman, McGlinchey, Chelminski, & Young, 2007) report evidence that total scores on a semi-structured clinical interview for assessing major depression were best represented as a taxon. The results of our simulation offer an alternative stance in the taxon-continuum debate, namely that MD is both a taxon and a continuum, depending on the connectivity of the network. More specifically, as one can infer from Figure 5.8, networks with weak connectivity appear to behave as continua: transitions from less to more MD symptoms and vice versa take place in a smooth, continuous fashion. That is, the network model for MD hypothesizes that in people resilient to develop episodes of MD, progressing from not having symptoms to many symptoms, and back, under the influence of stressors, is a continuous smooth process. On the other hand, networks with strong connectivity appear to behave as taxa: under the influence of stress, transitions from less to more MD symptoms and vice versa take place in a discontinuous with a ‘forbidden’ zone of rarity (between 1 and 5 symptoms) that does not seem to function as a stable state. This hypothesis is consistent with empirical findings that major depression appears to be a taxon in patient samples.
while a continuum in studies with community samples (which often contain many people that are resilient for developing depression; e.g., Baldwin & Shean, 2006; Ruscio et al., 2007; Ruscio, 2009; Slade & Andrews, 2005; Slade, 2007). Additionally, our hypothesis sits well with clinical observations that for patients prone to developing episodes of MD, their mood states indeed seem to fall in two distinct zones with a large gap between the two.

Diathesis-stress theory of major depression

The generic diathesis-stress model (Abramson, Metalsky, & Alloy, 1989; Bebbington, 1987; Beck, 1987; McGuffin, Katz, & Bebbington, 1988; Robins & Block, 1988) attempts to answer questions such as why some people develop MD after experiencing stressful life events while others do not. The model does so by positing that developing disorders such as MD is the result of an interaction between a certain diathesis (i.e., vulnerability) and a range of possible stressors. According to this model, the experience of a certain stressful life event can activate the diathesis, thereby “...transforming the potential of predisposition into the presence of psychopathology” (Monroe & Simons, 1991). Thus, the theory posits that some people are just more vulnerable than others and when put under stress, these people have a high risk of developing MD and experiencing relapse. Exposed to the same stress, those without this diathesis are at quite low risk.

A substantial problem with existing formulation of the diathesis-stress model is that despite many efforts to define diathesis, there is no universally accepted and proven hypothesis about what diathesis is: what do we mean when we say that a particular person is vulnerable? Does diathesis/vulnerability refer to some pathology that is predominantly (1) biological such as having lots of risk alleles, (2) developmental like having experienced sexual abuse as a child or (3) psychological such as having a relatively high level of neuroticism (Caspi et al., 2003; Ensel & Lin, 1996; Harris et al., 2000; Kessler & Magee, 1993)? Or, alternatively, is vulnerability a particular combination of these three pathologies, for example being sexually abused as a child which causes relatively high levels of neuroticism later in life? Additionally, there is no consensus about how diathesis and stress interact in bringing about an episode of MD (Belsky & Pluess, 2009; C. Hammen, 2005; Monroe & Simons, 1991): do stressful life events activate the diathesis (e.g., loss of a loved one results in the expression of risk alleles) or does diathesis act as a moderator (e.g., loss of a loved one results in the development of more MD symptoms in someone with lots of risk alleles than in someone without these risk alleles)?

Our network model of MD is a diathesis-stress model in that it both explicitly models vulnerability—which is, in our model, the overall strength of the connections in a given network—as well as the interaction between this vulnerability and the influence of stressful life events: stress augments the probability of symptoms to become ‘active’ resulting in one or a few symptoms becoming actually active; and when the connections in the MD network are generally strong, then these activated symptoms will result in the activation of other symptoms as well, eventually culminating in a full-blown episode of MD. As such, our model provides an alternative, concrete and testable interpretation of diathesis, stress, and the interaction between them; and our preliminary results are encouraging for this particular interpretation of the diathesis-stress model. Additionally, the results of our simulation show that the level of stress necessary to activate symptoms was decreasing with increasing connection strengths. As such, an additional testable hypothesis, for instance via time series modeling, would be that when a person is more vulnerable to develop an episode of MD (i.e., stronger intra-individual connections), less stress is needed to induce the activation of symptoms (possibly culminating in a full-blown episode of MD).
Treatment

The hypothesis, which we confirmed with simulations, that vulnerable networks (i.e., networks with strong connectivity) behave as a cusp catastrophe model potentially offers a new outlook on treatment: more specifically, the different therapeutic approaches for patients with MD can be categorized according to their effects on the MD system. First, a continuous force may be applied that reduces the whole set of stress parameter values. The aim would be to reach the lower left threshold that shifts the mood system back towards the healthy attractor. Many antidepressants may work through this mechanism. The metabolism or reuptake of monoamines (e.g., serotonin and norepinephrine) is blocked immediately after drug administration, while different antidepressants were shown to positively affect emotional processing in healthy subject already within one week (A. Frazer & Bennansour, 2002; Harmer, Shelley, Cowen, & Goodwin, 2004; Harmer, 2010). Yet, in many patients it takes more than 6 or 8 weeks to experience the full benefits of treatment with antidepressants (Quitkin, McGrath, Stewart, Taylor, & Klein, 1996; Trivedi et al., 2006). The hysteresis effect may help to explain the delay in antidepressant drug action. At critical thresholds, tiny disturbances may not only cause a large affective shift (i.e., a critical transition), but that shift is accompanied by a high degree of irreversibility (i.e., inertia). That is, the system can shift towards MD under the influence of a mild stressor, but if that same amount of stress is subsequently removed from the system, the system does not directly return to a healthy state. Second, a strong perturbation may be applied that ‘kicks’ the mood state of the MD system. In other large-scale complex systems with alternative attractors and tipping points, perturbations may tip the system into an alternative basin of attraction (Scheffer et al., 2009; van Nes & Scheffer, 2007). A perturbation increases the chance of arriving at another (more desirable) attractor. Sleep deprivation, the N-methyl-D-aspartate (NMDA) antagonist ketamine, and electroconvulsive therapy may destabilize a person’s basin of attraction, which may induce rapid (but often transitory) antidepressant effects (J. C. Gillin, Buchsbaum, Wu, Clark, & Bunney, 2001; Zarate et al., 2006). A third option from a theoretical standpoint would be to loosen or split the connections between the nodes of the MD network. This would transform the whole shape of the state space landscape, removing bifurcations and the hysteresis effect. Depressive symptoms would recede when the adverse influence of one activated node of the node would no longer transmit its effects to other nodes, and a more resilient state would be achieved. Cognitive behavioral therapy contains techniques that can help to desynchronize and loosen the connections between MD symptoms (see also Cramer et al., 2010): techniques that help a patient, when experiencing, say, depressed mood, to not easily let that depressed mood cause suicidal thoughts, for example by challenging the patient’s assumptions about the abnormality of suffering from depressed mood from time to time. Finally, combining these options might be most promising: loosening the connections between MD symptoms first, followed by reducing stress, may allow for a continuous and smooth path to euthymia. However, we are still at the first stages of exploring the use of the cusp catastrophe model in MD and therefore, these treatment options are merely theoretical at this point.

Discussion

We have shown that a model in which MD is characterized as a network of causally connected symptoms has the potential to explain what makes certain people vulnerable to develop an episode of MD: the stronger the connections between the symptoms of someone’s individual MD network, the easier it is for a full-blown episode of MD
to develop. Additionally, we showed that in the weakly connected networks (i.e., the hypothesized resilient networks/people) spontaneous recovery occurred, a well-known clinical phenomenon. The network model of MD also has the potential to explain why some people develop an episode of MD after (mild) stress while others do not; and why the shifts from depressed to healthy states and vice versa generally follow a non-linear pattern. More specifically, we have formulated a novel definition of diathesis in terms of the strength of connections between MD symptoms; as well as a novel hypothesis about the interaction between diathesis and stress: stressful life events influence individual symptoms directly and the diathesis then determines whether a cascade of symptom development emerges that can culminate in a depressed state. With simulated data, we have shown that our formulation of the diathesis-stress model works: resilient networks (i.e., with weakly connected symptoms) could handle significant amounts of stress without falling into a depressed state; while the vulnerable networks (i.e., with strongly connected symptoms) behaved like a cusp catastrophe: at tipping points, only slight amounts of stress sufficed to tip these networks into a depressed state.

There are some extensions of the model that might serve to test additional theories about the pathogenesis and maintenance of MD. For example, there is evidence for a reverse relation between stressful life events and MD in which the presence of depressive symptoms predisposes a person towards experiencing certain stressful life events (Maciejewski, Prigerson, & Mazure, 2000): e.g., experiencing fatigue and loss of interest resulting in the loss of employment. Our model could thus be extended by allowing symptom development to trigger the development of stress. Additionally, kindling—the phenomenon that stressful life events play the greatest role in the first onset rather than in subsequent episodes of MD—might be incorporated in the model by making the connections between MD symptoms stronger after every MD episode: that is, each consecutive episode makes the network more vulnerable. This extension of the network model would resonate with evidence suggesting that kindling does not necessarily mean that after the first onset, subsequent episodes come out of the blue; rather, such episodes are elicited by less and less severe life events (Monroe et al., 2006). As Kraepelin (1921) noted about one of his patients: she became depressed “after the death first of her husband, next of her dog, and then of her dove” (pp. 179). A final future extension of our model could be the incorporation of the fact that not all symptom dynamics take place within the same time scale. For example, it stands to reason that mood is a variable that can fluctuate within a time scale of hours; but that the relation between insomnia and fatigue unfolds over days (in most people, insomnia one day will not immediately cause fatigue the next day). And the relation between depressed mood and thoughts of suicide is likely an even slower dynamical process. These different time scales are currently not implemented in the model. Additionally, it might also be another source of intra-individual differences: it is possible that vulnerable people differ from healthy people in that the dynamics of the former group are on a faster time scale than the dynamics of the latter group. For example, it is possible that, ceteris paribus, in vulnerable people, depressed mood causes thoughts of suicide faster than in resilient people.

In this chapter, we used simulated data but naturally, testing the model with empirical data is needed in order to draw definitive conclusions. What kind of data would we need for such testing? We cannot stress enough that time-intensive data is key in testing many, if not all, assumptions of network(-like) models. More specifically, one would need intra-individual data in which individuals are followed for a long period of time and are asked about life events, minor daily hassles and symptoms at multiple time points per day. Experience Sampling with data collection through electronic diaries and smart phones would be a particularly suitable method for collecting such data (Myin-Germeys et al., 2009). With such data, it becomes possible to estimate network parameters for
individual people and to test whether intra-individual networks with strong connections are indeed vulnerable to the impact of relatively mild stressors. Also, one would expect that resilient people, when suffering from some symptoms due to a stressful life event, have a higher probability of recovering spontaneously than vulnerable people. Finally, one could also further test the hypothesis that in vulnerable people, MD is a taxon while it is a continuum in resilient people.

If an extended model based on empirical data would confirm that vulnerable networks (i.e., networks with strong connections) behave according to the dynamics of a cusp catastrophe, what would the implications be? For one, a cusp catastrophe implies the existence of tipping points. Finding these tipping points for individuals’ networks could then prove beneficial for two reasons. First, knowing that someone’s MD system is close to tipping from a healthy to a depressed state would allow for precisely timed therapeutic interventions that might prevent such a catastrophic shift. Second, on the other hand, knowing that someone’s MD system is close to tipping from depressed to a healthy state would offer the opportunity of giving the system a large kick (e.g., sleep deprivation) at exactly the right time so that the system, like the ball in the bowl, is kicked out of the depressed attractor and ends up in the healthy attractor. Thus, the tipping points in the cusp catastrophe model might help in predicting when prevention and intervention have the highest probability of success.

But how does one find these tipping points? Recent findings suggest that all catastrophic systems, from financial systems to the climate, display early warning signals that a system is approaching a tipping point (Carpenter & Brock, 2006; Dakos et al., 2008; Fort, Mazzeo, Scheffer, & van Nes, 2010; van Nes & Scheffer, 2007; Scheffer et al., 2009). One such early warning signal is called critical slowing down: right before a tipping point, the system is getting slower in recovering from small perturbations. Pertaining to MD, for instance, one might see that someone has more difficulty than usual to recuperate from a minor daily hassle like an unpleasant day at work. Numerically, this slowing down can be traced by inspecting autocorrelations: the correlation between scores of the same variable at multiple time points (e.g. the correlation between 60 measurements of depressed mood). Such autocorrelations go up when the system slows down: slowing down means that at each time point, the system much resembles the system as it was at the previous time point, meaning that the autocorrelation is relatively high. With time-intensive intra-individual data it will become possible to inspect autocorrelations and other potential signals that someone is in critical danger of developing an episode of MD or that a healthy state is within reach.