Symptom network models in depression research

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CHAPTER 1

INTRODUCTION

When you start thinking about networks, you can see them all around. Take for example a collaboration network of some large company with several departments. You can envision employees being nodes in a network and draw a connection between those who often work together. Those who work at the same department will probably have many connections amongst each other. In addition, some employees who work in projects that transcend departments, will have connections with employees outside their own department. This *social* network can be further analyzed. If the network is dense (i.e., contains many connections), many employees collaborate and, consequently, knowledge will spread easily through the department or company. A less dense network, however, means that people work more solitary. Next, one could zoom in on individual employees: Which employee collaborates most with other employees in his or her department? Which employee collaborates most with employees outside his or her department? In terms of spreading of knowledge, a company will benefit most from employees who collaborate with many other colleagues within and between departments, as they enable spreading and/or acquiring knowledge most efficiently. Analysis of these patterns of connections between individuals is known as network analysis.

1.1 The network perspective on psychopathology

Besides the social sciences, network analysis has also entered research on intelligence, and psychopathology (Borsboom, 2008; Borsboom & Cramer, 2013; Cramer, Waldorp, Van Der Maas, & Borsboom, 2010; Schmittmann et al., 2011; Van Der Maas et al., 2006). Focusing on psychopathology, the nodes in the network are now symptoms instead of employees, and the connections — called *edges* in graph theory — are now relationships between symptoms. For example, when a person does not sleep well for several nights, he or she will get tired. Although this may be an experience that many people have, it can get out of hand for some. A possible causal chain could be: insomnia → fatigue → concentration problems → feeling sad → insomnia. Ultimately, this could culminate in a full-blown major depressive disorder (MDD). Following from this network view on psychopathology, stronger and/or more causal relationships (i.e., stronger connectivity) can more easily lead to MDD. That is, if Bob′s symptoms have strong causal relationships, his insomnia can culminate easily in MDD. Conversely, if Alice′s symptoms have weak connectivity, her insomnia does not lead to MDD; the sleep problems can subside without having triggered activation of symptoms in a causal chain.

1.2 This thesis

Although the network perspective is a relatively new game in town — with its conceptual and empirical foundations in 2008 and 2010 (Borsboom, 2008; Cramer et al., 2010) and the development of an advanced visualization technique in 2012 (i.e., the free R package qgraph; Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012) — its popularity is rising fast. Therefore, when this PhD project started in 2012, it was important to contemplate about what the network perspective could offer psychology and psychiatry. An inspiration for this search was a simulation model I made already before this project started. In this interactive agent-based simulation tool, depression is modeled as a network of its symptoms (Van Borkulo, Borsboom, Nivard, & Cramer, 2011; Wilensky, 1999)[1]. Investigating the behavior of this relatively simple model raised question about what it could be in networks that could give rise to behavior in real people: the connection

[1] see Van Borkulo, Van Der Maas, Borsboom, and Cramer (2013) for an advanced interactive model

strengths, connectivity, how *easy* symptoms develop? This was the starting point of this thesis.

The work described in this thesis is part of a broader collaboration between the University Medical Center Groningen (Dept of Psychiatry) with the largest provider of mental health services in the Netherlands (i.e., GGZ Friesland) focusing on novel data driven approaches to improve the effectiveness of mental health care. It is also the result of a fruitful collaboration with the Psychological Methods department of the University of Amsterdam who have done pioneering work on the network approach to psychopathology. It is organized around four components: 1) a theoretical deepening of the network perspective on psychopathology, 2) the development of methodology to analyze group-level data, 3) empirical studies at the group-level, and 4) individual networks and prediction. In the following, I will describe these components in more detail.

1.2.1 A theoretical deepening of the network perspective on psychopathology

First, in **Chapter 2**, the network perspective is introduced. Moreover, this chapter elaborates on graphical models, which are used to model symptom-symptom relationships. In addition, this chapter describes how to analyze networks to discover important symptoms and symptom dynamics in a network. **Chapter 3** elaborates on the implication of the network perspective for research in psychopathology. Currently, we do not fully understand why some healthy individuals develop MDD whereas others do not while experiencing similar adverse events, or why some patients recover from MDD whereas others do not. Therefore, this chapter investigates vulnerability from a network perspective by simulating data from a network structure that was partly based on empirical data. This chapter aims to study 1) differences in the number of depression symptoms of more and less strongly connected systems, and 2) differences in behavior of such systems when putting them under *stress*.

1.2.2 Methodological challenges for group-level analyses: network estimation and comparison

In a next part of this PhD project, we wanted to investigate whether vulnerability to develop or maintain MDD is related to network connectivity in cross-sectional data (i.e., at the group-level). However, at the time, there was no methodology at hand to infer the network structure of psychopathology from empirical data. That is, a big difference with networks such as the collaboration network is that a psychopathology network is *unobservable*. You cannot ask a symptom whether it has a causal relationship with another symptom. Also, a psychopathology network is not like a road infrastructure in which you can only go directly from one city to another, if there is a road — that you can actually *see* — between them. The network structure of psychopathology, which can consist of (temporal) associations between symptoms, has to be inferred from measurements of symptoms. This requires a method to estimate the network structure. Consequently, applying network analysis to psychopathology is not a trivial thing and poses a great challenge on studying psychology and psychopathology from a network perspective. **Chapter 4** introduces a method, called *eLasso*, to estimate the network structure from binary data. Performance is studied with simulations and the method is illustrated with real data. For a tutorial about how to use the implementation in R package IsingFit, see Appendix D.

A next step in investigating vulnerability, is to compare network structures of groups of individuals who differ with respect to this. **Chapter 5** presents a test to statistically compare networks: the Network Comparison Test (NCT). This test compares two networks on three different characteristics. Performance of NCT is also studied with a simulation study and the utility of NCT is demonstrated with real data. For a tutorial about how to use the implementation in R package NetworkComparisonTest, see Appendix E.

1.2.3 Clinical studies relating vulnerability to local and global connectivity of group-level networks

Having developed this methodology, we will then investigate the relationship between network structure and course of depression in empirical data. **Chapter 6** examines whether there are differences in network structure of patients with

persistent versus remitted MDD. In a prospective study, global network structures are compared in patients at baseline, in which those who will recover and those who will not at 2-year follow-up are contrasted (see also **Chapter 7**, which contains a comment and reply to this study). Conversely, **Chapter 8** considers whether local symptom network connectivity (centrality) of healthy individuals was related to the risk of developing MDD. We investigated healthy individuals with no lifetime MDD and related symptom centrality of the group-level network to the risk of developing MDD at 2-year follow-up.

1.2.4 Methodological challenges at the level of the individual: using network models to predict clinical course in patients with depression

After having focused on group-level analyses, we zoom in on individual networks in the next part of this thesis. **Chapter 9** proposes a method to predict the behavior of an individual′s network structure. The ratio between *activation* and *recovery* of symptoms — expressed in the *Percolation Indicator* (PI) — is hypothesized to predict the behavior of the symptom network in the future. Performance of PI is investigated and the method is illustrated with real data.

1.2.5 Conclusions

To summarize results of the entire field of empirical studies that applied the network perspective to psychopathology, **Chapter 10** encloses a review of all such studies from 2010 — when the empirical foundation was laid – to 2016. The empirical studies are discussed in the light of three empirically relevant themes: comorbidity, prediction, and clinical intervention.

Finally, **Chapter 11** contains an overview of the results of this thesis, accompanied by a general conclusion. Although the network approach has gotten very popular and a lot has been accomplished in the field in a relative short time, there are still many questions to be answered. Therefore, this thesis concludes with a proposed research agenda for the future of the network perspective on psychopathology.