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Networks and psychopathology

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Chapter

General Introduction

1

Major Depressive Disorder (MDD) is a highly impactful mental disorder that thus far has eluded understanding and is projected to become one of the most significant contributors to the global burden of disease (Mathers and Loncar, 2006). MDD is hard to treat and research because it is a highly heterogeneous illness. Heterogeneity is present in various facets, or modes, of MDD (Sullivan *et al.*, 1998; Shafer, 2006; Rhebergen *et al.*, 2012; van Loo *et al.*, 2012). Patients with the same diagnosis may display a variety of symptom profiles, display different illness course trajectories and may react differently to various treatment options. Put differently, there exists heterogeneity in the person, symptom and time mode of MDD. Moreover, there exists no reliable biological marker or indicator for MDD.

The definition of depression as given by the Diagnostic and Statistical Manual of Mental Disorders (DSM) is insufficient as an explanatory device (Frances and Widiger, 2012). Although the DSM may have been useful in a time without standardization when each psychiatrist had his or her own idea on what constitutes depression, its use becomes problematic when it is relied upon as a definitive description. The DSM definition of MDD creates an umbrella concept that captures a large variety of possible symptom profiles. Using the DSM definition alone, there are 425 possible symptom profiles that constitute MDD but up to 16400 profiles exist if other/additional criteria are applied (Fried *et al.*, 2017).

From a statistical standpoint, MDD as a construct has been hard to elucidate as well. While the abovementioned sources of heterogeneity are clear, the statistical methods traditionally used in psychiatric research, latent variable models (Singh, 2006), make unrealistic assumptions about the illness they intend to model.

In latent variable models (LVMs), collections of measurable variables are modeled as being solely dependent on one or more unobservable latent variables.

Specifically, it is assumed that these measurable variables are mutually independent from each other. One of the problems with the use of LVMs in psychiatric research is this fundamental assumption about the relationship between the measurable and latent variables. In a psychiatric research context, the measurable variables might represent items on a depression questionnaire and the latent variable(s) represent the underlying illness. Here, the assumption of mutual independence between items is unrealistic since there is good reason to assume there exist more direct connections between symptoms (Cramer *et al.*, 2012; Borsboom and Cramer, 2013). Furthermore, it is not evident that there is a single latent construct representing depression; i.e., whether there exists 'an underlying disease' at all. A final limitation of the LVM approach is that it typically focuses on only two out of three (time, symptom, person) modes: LVMs are used to either cluster persons based on their symptoms (i.e. in cluster analyses) or to cluster symptoms based on their (co)variation across persons (i.e. in factor analyses).

The network approach to psychopathology is a proposed alternative to the LVM perspective of mental illness (Cramer *et al.*, 2010; Borsboom *et al.*, 2011). This approach lets go of the latent variable assumptions and instead studies mental disorders as a network of symptoms. In this approach, a network is comprised of a collection of nodes, representing (depression) symptoms, and edges between nodes, representing associations between these nodes. One reason motivating the development of this approach is the fact that symptoms of depression do not manifest all at once, but normally arise over time, which is likely to result from a causal interplay between symptoms. For example, one could imagine a person who experiences stress at work. This stress might inspire episodes of excessive rumination, which in turn might cause a drop in sleep quality, possibly leading to increased irritability and feelings of guilt, eventually leading to a full-blown major

depressive episode. The network approach allows researchers to focus on inter-symptom relationships and characteristics of these symptom networks. Ideally, insights into mental disorders can be obtained from these networks and/or characteristics.

Psychiatry is one of the latest additions to a sizable list of scientific disciplines that have started to utilize networks to model phenomena. Scientific investigation of networks, in particular the mathematical analysis of networks (which is also known as graph theory), can arguably be said to have started with Euler in 1736 (Shields, 2012). However, it was not until the beginning of the 20th century that network science became a mature scientific discipline (Barabási, 2012) and found applications in areas such as sociology (van Meter, 2005), biology (Barabási and Oltvai, 2004), medicine (Barabási, 2007) and computer science (Karp, 1960). In psychiatry, network models appeared in 2010 with the work of Denny Borsboom (Cramer *et al.*, 2010; Borsboom *et al.*, 2011). Networks (also known as graphs) also appear in statistics, where their marriage with probability theory results in a type of model called a graphical model (Almond, 2010a). Here, the nodes in a network represent random variables and edges between the nodes represent measures of statistical association (e.g., conditional probabilities, (partial) correlations or regression coefficients). Graphical models are useful in detecting dependencies between large numbers of random variables, which may otherwise be hard to accomplish. For example, suppose we obtain measurements from n binary random variables (x_1, \dots, x_n) . In order to estimate the associations between them, even though we only deal with binary variables, we already need to estimate 2^n probabilities. When variables have more than two levels, this problem would be even larger.

An advantage of graphical models is that they have connections to other, more familiar statistical methods. For example, in the case of multivariate Gaussian graphical model, estimating a network of conditional dependencies between variables amounts to inverting their sample covariance matrix (Almond, 2010a) (see chapter 5), the result of which is known as the sample precision matrix. The network structure can then be read off this precision matrix; two random variables are conditionally independent if and only if the corresponding entry in the precision matrix is zero. Networks have a close relationship with vector autoregressive (VAR) models as well (Dahlhaus & Eichler, 2003). The values in the regression coefficients matrix of a VAR model correspond to the edge weights of a directed network.

Networks are used in cross-sectional studies (where the edges are lines and we deal with an undirected network) as well as longitudinal studies (where edges are arrows and one can distinguish between a node's ingoing and outgoing edges, also known as a directed network). Since in statistics, and psychiatric epidemiology in particular, edges typically represent a statistical measure of association, they almost always have a weight, resulting in what is called a weighted network. The weight reflects the strength of the association. In cross-sectional studies, networks have been used to model (partial) correlations between Likert-type items (Borsboom and Cramer, 2013; Bos *et al.*, 2018) or activation thresholds in Ising models (van Borkulo *et al.*, 2014). In longitudinal studies, networks have been used in combination with VAR models (Bringmann *et al.*, 2018) and mixed linear models (Bringmann *et al.*, 2015). For an oversight of the state of the network approach in mental health research, see Fried *et al.* 2017a.

While networks form an interesting new approach to understanding mental health in general and depression in particular, it is still an area of research in its infancy. A number of conceptual and technical issues have remained unsolved so far. For

example, typical network studies focus on a relatively low number of items out of computational necessity or lack of degrees of freedom. Often, authors fix certain model parameters, for example random effect parameters and their covariance structure, to make the model fitting process converge (Wigman *et al.*, 2015; Klippel *et al.*, 2017; Snippe *et al.*, 2017). This is unfortunate since one of the main selling points of networks in statistics is that they can represent associations between a high number of variables. Another issue is that measurement tools in psychiatric epidemiology typically provide Likert-type data, which display a number of departures from network modeling assumptions. Particularly, these data can be skewed, display floor or ceiling effects (e.g., for an item such as suicidal ideation), or not adhere to the assumption of normality in other ways. This problem is especially common if items are used to assess negative affect or symptoms in relatively healthy populations with a strong positive skewness and floor effects (e.g., Wigman *et al.*, 2013; Pe *et al.*, 2015a). Violations of these assumptions may have large consequences (Terluin *et al.*, 2016). Another issue in network research is that it is not entirely clear what characteristics of a network are most important for a medical researcher or clinician. It has been postulated that a network with a large number of connections or stronger connections represents a higher level of psychopathology (Borsboom, 2017). However, empirical evidence supporting this hypothesis has been inconsistent thus far (Forbes *et al.*, 2017). Some studies indeed found a higher network density in depressive patients compared to healthy controls (e.g., Pe *et al.*, 2015a; Wigman *et al.*, 2015; Wigman *et al.*, 2013a), but other studies did not (De Vos *et al.*, 2017; Snippe *et al.*, 2017; Bos *et al.*, 2018; Groen *et al.*, 2019; Schwaren *et al.*, 2018) and it is not unlikely that some of the positive findings are due to differential floor effects in depressives versus healthy controls (Terluin *et al.*, 2016). Also empirical results of other network characteristics, like the presence,

direction, strength or centrality of individual symptom nodes, have been rather inconsistent thus far, which has led to serious doubts about the replicability of network results (Forbes *et al.*, 2017a; Steinley *et al.*, 2017).

In this thesis, I look at possible solutions to some of these problems. Specifically, to address the problem of overly complex models, I will explore the potential of a so-called *sparse* version of a dynamic network model that would allow for a larger number of variables. To address the problem of non-normality, I will consider the use of a network model that allows for the modeling of non-normally distributed data, while retaining the ability to model dependencies between items. Furthermore, this thesis illustrates the network approach in general and its use in psychiatric research in particular, and presents findings from samples of depressed, psychotic and multiple sclerosis patients. Finally, I will discuss the possible meaning of network analyses, the strengths and weaknesses of the network approach, and, based on the presented findings, will reflect on the biggest challenges and opportunities in the field.

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