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## Networks and psychopathology

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**Chapter**

General Discussion

**7**



In this chapter, I summarize the findings presented in the previous chapters, integrate and compare them with other contemporary network research and discuss potential pitfalls, opportunities and possible future research directions in the psychiatric network field.

### Summary

The network approach, as an alternative to the traditional latent cause conceptualization of mental illness (chapter 2), is an intuitively attractive new field that has given researchers in epidemiology, psychiatry and related areas a sizable, 'shiny' new toolbox of methodological concepts, with which to analyze item-response data. A subset of this toolbox is displayed in chapter 3, where we used the Ising model and the concept of network communities, i.e. the concept of detecting which nodes in a network belong together, to study data from children with and without psychotic and related experiences. Focusing on communities allows one to uncover different ways of grouping symptoms than according to their original domain. Moreover, this analysis showed that, using the network approach, it is possible to extract additional information from data that cannot be obtained from composite scores. For example, mean item scores were similar for negative and depressive experiences, while nodes in the negative experience subscale showed a higher level of interconnectivity.

Longitudinal sparse vector autoregressive models were used in chapters 4 and 5. In chapter 4, a sample of depressed patients was compared with a healthy sample that was matched on age, gender, smoking behavior and BMI. This study showed that longitudinal network connectivity was strongest in the healthy group when sparse vector autoregressive (VAR) and a data transformation to counter non-normality were used. However, network connectivity was strongest in the MDD

group when a standard multilevel model and no transformation was used. This points towards the importance of data pre-processing steps for the eventual interpretation and interpretability of (longitudinal) network models in psychiatry. Sparse VAR models were used in chapter 5 to investigate and compare emotion dynamics in a group of patients with multiple sclerosis and a general population sample that was pair-matched on severity at baseline. This study showed that networks of MS patients and general population individuals with roughly similar levels of psychopathology at baseline, have a different architecture: i.e. the symptom nodes have a different centrality. Both studies revealed that utilizing regularization is a handy and sometimes necessary tool to estimate networks, but also has some disadvantages, such as the instances where it leads to ‘empty’ networks.

Chapter 6 shows a novel approach to the issue of mental illness subtype detection. This chapter shows that non-parametric clustering of individuals based on inter-symptom associations results in groups with distinct levels of psychopathology as well as different network representations. It also shows the usefulness of a semi-parametric network estimation technique for non-normally distributed data.

### **Integration with contemporary network research**

As mentioned in the introductory chapter of this thesis (chapter 1), network research suffers from a number of technical and conceptual issues, some of which I have aimed to address in this thesis.

The first issue is overparametrization: the lack of degrees of freedom in the estimation of networks. This problem occurs especially in dynamic networks and multilevel models with multiple nodes. For example, a common way to estimate a dynamic network on the basis of time-series data obtained through Experience

Sampling Methodology (ESM) is to use a multilevel VAR model with random effects for all parameters and an unstructured random effect covariance matrix (e.g., Wigman *et al.*, 2015, Bringmann *et al.*, 2013, Bringmann *et al.*, 2016, Pe *et al.*, 2015, chapter 4). One downside of this model is that, as the number of items increases, the number of parameters that need to be estimated increases rapidly. In that case one may need to (i) reduce the number of nodes in the network, (ii) impose additional structure on the covariance matrix of the model (iii) remove random effects from the model, or (iv) collect more data. Depending on the circumstances, these solutions can be difficult or infeasible, may lead to biased estimates, or do not do justice to the heterogeneity present in the data. The assumption that dynamic effects are identical across all individuals is unrealistic was also shown in our chapters 4 and 5, in which our analyses at the individual level showed between-person heterogeneity in the effects. In chapters 4 and 5 we showed that the use of regularization is one possible solution to the problem of overparametrization, although this method has strengths as well as weaknesses. One observed strength was that we could estimate a larger network compared to multilevel-based networks. A downside of this approach was the fact that standard information-theoretical approaches to regularization-parameter selection (i.e. by using the AIC or BIC) led to almost empty networks in chapter 4. Another downside is that, although we were able to fit networks at the group level and at the individual ( $N=1$ ) level with this sparse VAR model, there is no multilevel implementation of this model. This could be problematic since fixed-effect models may not accurately display the heterogeneity present in MDD. Future research might focus on designing and implementing a model that allows for the estimation of sparse dynamic networks using VAR while also incorporating random effects.

The second issue we aimed to address in this thesis is non-normality, which arises from the type of data we often use in our field (i.e. discrete Likert-type data) and the type of ‘non-normal’ phenomenon we aim to measure. Specifically, when measuring depression or related disorders, one often measures symptoms that typically display low variance, such as suicidal ideation. Moreover, the frequency of occurrence of symptom variables in relatively healthy samples is often low, leading to floor effects and skewed data distributions. Modeling data with such non-normal distributions may lead to biased estimates (Terluin *et al.*, 2016; Forbes *et al.*, 2017a). Particularly, it may lead to deflated regression coefficients in healthy samples compared to depressed samples, because the standard deviation in the former samples is lower. In chapters 4, 5 and 6 we employed a probability integral transformation to transform skewed data in order to better meet distributional modeling assumptions. One upside to this preprocessing step is that this data transformation is empirically determined instead of based on assuming a specific a priori functional form, in contrast to skewness-compensating approaches like the one proposed in (Terluin *et al.*, 2016) where a generalized mixed model with an inverse Gaussian link function is used. Another upside to this procedure is that it is not part of the statistical model but takes place before any model fitting happens. The downside is that it might impede interpretation of results, since we are doing inference on transformed data.

The third issue is the hypothesis that network density is associated with a higher level of illness severity. For example, in Van Borkulo *et al.* (2015) it is reported that people who persist in their depressive state will display a network with a higher density. Pe *et al.* (2015) found that people with MDD have a more densely connected network compared to the network of a sample of healthy controls. Wigman *et al.* (2013) found severity groups that were characterized by

progressively increasing connection strength and Wigman *et al.* (2015) found a more strongly connected dynamic network for persons with a clinical diagnosis compared to healthy subjects. In chapters 4 and 5 we could not confirm this hypothesis, and also other recent studies could not (e.g., Snippe *et al.*, 2017; Schwaren *et al.*, 2018; Groen *et al.*, 2019; Bos *et al.*, 2018). In chapter 4, we saw that data preprocessing steps such as standardization and transformation, and whether this is done at the group or the individual level strongly influences the density comparisons. In view of the fact that estimates of connection strength are sensitive to differences in standard deviations, as exemplified above, it seems that especially transformation or other methods to deal with floor effects may impact the conclusions drawn from such comparisons. In order to draw definitive conclusions based on network analysis it seems that methodological agreement on this matter might need to be reached first.

A final issue is the actual definition of network 'density'. In most network studies in psychiatry (e.g., Bringmann *et al.*, 2016), network density is defined as the average of the absolute values of the edge weights in the network of interest. This is in contrast with the standard definition of network density in graph theory, where density is traditionally defined as the fraction of the number of realized edges to the total possible number of edges (Coleman and Moré, 1984). These different density measures may yield different results (e.g., chapters 4 and 6). This does not mean that either definition is wrong per se and one can make arguments for both. On the one hand, a possible downside of the 'density as average connection strength'-operationalization is that this definition implies that an empty network with one very strong connection could have a larger density than a network with lots of weaker edges. On the other hand, there is no reason to assume that the classical operationalization of density is better. It might be that both definitions



capture meaningful, but provide different information about a network. Again, this issue points to the need for more methodological clarity and agreement. The same can be said about local connectivity measures such as strength, betweenness and closeness. In cross-sectional networks Forbes *et al.* (2017) advocate to only focus on strength because it is not clear that the other two node characteristics actually represent anything psychopathological and perhaps the same can be said about global network characteristics. As for longitudinal networks, a commonly used centrality measure is in- and out-strength but I am not aware of any evidence that would lead one to prefer a particular centrality measure over another.

### **Challenges, opportunities and future research**

Because the network approach is a relatively new avenue of research, there is a multitude of future research that can be done. The issues that need to be addressed can be roughly divided into a methodological, practical and a conceptual category, although the boundaries between these categories can be fuzzy. Concerning methodological issues, there are some limitations to network models that are currently commonly used in psychopathology research. For example, most network models assume either a continuous, Gaussian probability density (e.g., VAR models, Gaussian Graphical Models) or random variables with a binary outcome (e.g., van Borkulo *et al.*, 2014). However, the typical data that psychopathology researchers work with are neither. Since data are often in the form of Likert-type scales, it would be helpful to utilize network models that can model non-Gaussian and/or discrete data with more than two levels. There is a model in statistical physics called the Potts model (Wu, 1982) that might be used for Likert-type data, but in the case of Gaussian networks there is still the matter of treating Likert-type data as continuous. The alternative would be to transform the data, as we did in multiple

chapters in this thesis, but the downside is that inference on transformed data is needed. Some work has been done on this topic (e.g., Morrison *et al.*, 2017), but it might be a while before there is a ready-to-use R package for such a model.

Another possible methodological topic for future research is the combination of multilevel network models with a regularization feature function. This would allow for estimating a larger number of nodes as well as modeling heterogeneity in the estimates, while also taking care of the rapidly increasing number of parameters in such a model. Another opportunity is in the area of time-varying network models. Recent research (Wichers *et al.*, 2018) on the link between complex systems theory and psychopathology suggests that symptoms may display sudden, non-linear shifts in system behavior. This points to the need for statistical models that can represent these aspects and some work has been already done on this topic (e.g., Bringmann *et al.*, 2017). Perhaps new techniques like these can model abrupt changes in mental states over time more accurately. Because depression may have biological and social causes (Kendler, 2014), the network approach might also be improved if research would combine data sources from other domains than self-report alone. This has been done as a proof of concept by Santos *et al.* (2017), but the authors note that, in their case, the employed methodology (a Gaussian Graphical Model with regularization) likely leads to under-pronounced edges between symptom and biomarker nodes.

The clinical relevance of network models is one practical issue that may be addressed in future research. Since the introduction of networks to the field of psychiatry there has been the hope that network models could deliver a patient's therapy plan, tailored to that specific individual. In fact, the application of networks in daily clinical research was recently investigated by Epskamp *et al.* (2018).

However, as was mentioned in Wichers *et al.* (2017), we ought to be careful. Although the methodology to estimate intra-person cross-sectional and longitudinal networks exists, one may wonder if the patient in question ends up looking at an accurate depiction of their symptom profile or just at a collection of statistical artefacts because the network approach is still in an early stage and only little is known about their functioning and robustness. Another practical challenge is the investigation of actual real-life predictive ability and/or usefulness of networks; how well do they predict when compared to existing clinical predictors and or clinical judgement? Such research could for example look into questions such as: how predictive are patient-specific local or global network characteristics of future remission, and how does this compare to the prognosis made by the clinician and/or established prognostic tools? It is important to understand how well network models map onto reality before we accept them into daily clinical practice.

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Finally, we come to the conceptual challenges. First, there is the issue of replicability and generalizability. According to Forbes *et al.* (2017), the network approach suffers from a lack of replicability, which they argue results from an abundance of measurement error, the exploratory nature of the methods and the large number of parameters to be estimated. One additional problem is that many network studies use different samples, experimental designs and questionnaires that can impact the resulting analyses (Fried *et al.*, 2017). Moreover, network models most often use self-reported single-item symptom assessments as their nodes. By doing this, all variance in each of the items is automatically assumed to be meaningful, whereas in reality a considerable portion of the variance in each individual item score will consist of patient- or sample-specific measurement error. This means that in practice it is unclear to what extent a network models

meaningful information and to what extent noise. Given that networks can be very sensitive to the above-mentioned methodological issues it is not very surprising that there is a replicability problem. Psychiatric research is quite hard from a statistical perspective. The ‘thing’ that we are interested in can usually only be measured by proxy. This measurement is a complex process in which many influences play a role that are outside the control of researchers. We have to remain well aware of this when interpreting network models or when designing a study.

As mentioned earlier, the network approach gives researchers a lot of new tools with which to analyze networks. With such a plethora of options, it is not a trivial matter to decide which tool is the best for the job. Moreover, it might not even be clear what that ‘job’ would be. What exactly does it mean to say that the network approach is a successful one? If one wants to know which tools are the best, then we need to first define an objective that we seek to maximize. Currently, it is not entirely clear what this objective should be. Do we need networks to be able to predict clinically relevant features, do we need networks to say anything etiologically relevant, or do we primarily need networks to produce a pretty picture? This is a question that demands topic-specific information and cannot be left to statistics alone.

Although an interdisciplinary approach to mental health seems to make a lot of sense in general given the mysteries of MDD, there exist some possible challenges with interdisciplinary psychiatric research: many concepts and tools are derived from other fields. For example, the Ising model as used by van Borkulo *et al.* (2014) is borrowed from statistical mechanics, where the notion of the energy of a system is used. This leads to the question if and how this concept actually maps onto

psychiatric concepts. Another possible problem with the tendency to use innovative tools from other (technical) fields lies in transparency. If a network paper contains a justification for some modeling choices by referencing mathematical papers, it is may be that the reader (who likely has a medical or psychological background) will not follow the reasoning and will have to assume that the argument is valid, while much may depend on these seemingly minute choices. I would argue that psychiatric research would benefit from using less complicated models, not more. Given the fact that psychiatric research already has a problem with replicability, one should be careful to add even more possible idiosyncrasies via new methodological features. Moreover, it seems that the lure to the shiny and well-filled network toolbox leads different researchers (myself included) to each pick different tools, leading to replicability issues. However, the research field is still quite young and it is perhaps not surprising that the first wave of research has mainly been exploratory in nature. For now, it seems that the biggest challenges in the field are not necessarily the ones that require new state-of-the-art models but rather lie in finding a well thought out, state-of-the-art approach to determine when and how to use network models in psychopathology research and how to ensure their applicability and replicability.

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