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Bouncing back from life's perturbations: Investigating psychological resilience through simulations

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"Systems thinking leads to another conclusion, however, waiting, shining, obvious, as soon as we stop being blinded by the illusion of control. [...] The future can't be predicted, but it can be envisioned and brought lovingly into being. Systems can't be controlled, but they can be designed and redesigned. We can't surge forward with certainty into a world of no surprises, but we can expect surprised and learn from them and even profit from them. [...] We can't control systems or figure them out. But we can dance with them!"

Donella H. Meadows
Thinking in Systems: A Primer, 2008, p 168-170.

CONTENTS

1

GENERAL INTRODUCTION

This chapter is partly adapted from the following book chapter:
Lunansky, G., Nuijten, M., Deserno, M., Cramer, A.O. J. & Borsboom, D. (2017). Psychologische stoornissen als complexe netwerken. In *Handboek persoonlijkheidspathologie* (pp. 245-266). Bohn Stafleu van Loghum, Houten.

1.1 INTRODUCTION

Mental disorders are the leading cause of disability worldwide, affecting more than 300 million people (World Health Organization, 2017). Major Depression (MD) alone is ranked as the single most significant contributor of non-fatal health loss globally (World Health Organization, 2017). Mental health problems place a considerable burden on the lives of suffering individuals, such as lower quality of life and an increased risk of experiencing adverse events (e.g., job loss, divorce, and lower life expectancy; Cuijpers et al., 2012; Lopez et al., 2006). In addition, mental health problems can have a long-lasting and severe impact on the social environment of the inflicted person and society as a whole (Greenberg et al., 2015). Stressful life experiences and adversity (e.g., the death of a loved one, abuse, physical illness, and poverty) are essential factors in initiating the development of mental disorders (Brown et al., 1987; Green et al., 2010; Kalisch et al., 2019).

However, not all people that face adversity develop persisting mental health problems. Around 90% of people in Western countries experience at least one potentially traumatizing event during their lifetime, but the lifetime prevalence of posttraumatic stress disorder is only about 8% (de Vries & Olff, 2009; Kilpatrick et al., 2013). In the immediate aftermath of a stressful life event, depressive symptoms occur quite frequently (e.g., 25% according to Cénat & Derivois, 2014), but many initially afflicted people return to healthy physical and psychological functioning (Bonanno et al., 2004). Why do some people seem to 'bounce back' quite rapidly while others get stuck in a whirlwind of problems and suffer from mental health complaints? Based on the Latin verb *resilire*, which means 'to spring back' or 'to rebound', *resilience* refers to the ability or capacity to maintain or quickly return to normal psychological functioning after facing some adverse event (Bonanno, 2004; Kalisch et al., 2017; Werner, 1995). Understanding resilience could help identify the mechanisms that help prevent or reduce the risk of developing mental disorders in people who have faced hardship. Therefore, resilience research is crucial to understanding how mental disorders can be hindered or prevented in the face of adversity.

Although various definitions exist, resilience is always defined in response to adversity. Therefore, the concept of resilience is a *disposition,* which expresses a tendency or capacity that manifests under certain conditions or situations (Mumford, 2003). Resilience refers to a response after facing adversity, begging the question how to scientifically study a person's resilience. Naturally, adversity cannot be induced or manipulated in experimental research for ethical reasons. Researchers have studied resilience in people who have faced adversity (e.g., childhood trauma) by following them over some time to see whether they developed mental health problems (e.g., see: Werner, 1993; Arseneault et al., 2011; Singham et al., 2017). In addition, researchers focused on healthy participants and investigated which positive factors (e.g.,

cognitions, behaviors, or traits) could be related to resilience (Simeon et al., 2007). While this type of research contributed substantially to the literature, such as which factors can play a part in accelerating or hindering the development of mental health problems, no strong predictors of resilience have been found (Bonanno, 2021).

There are more reasons why it is difficult to study resilience. Researchers have found that people can successfully adapt to the stressors they encounter (the *steeling effect*), or develop lasting problems making them more vulnerable to a minor stressor in the future (the *scarring effect*; Rutter, 2012; Wichers et al., 2010). Resilience should therefore be studied from a developmental perspective (Stainton et al., 2019) and is often described in terms of a dynamic process, in which the person is successfully adapting to its environment and stressors (Ioannidis et al., 2020; Kalisch et al., 2017; Rutter, 2012; Sapienza & Masten, 2011). This dynamic approach to resilience implies that a person's level of resilience can change over time, meaning that someone may be 'resilient' at one point in life but not at another point. Additionally, one may show resilience against one type of adversity (e.g., losing one's job), but not against another negative event (e.g., losing one's parent). These fluctuations in resilience are associated with different *protective factors* (e.g., optimism; Ellis et al., 2017) and *risk factors* (e.g., neuroticism; Roberts & Kendler, 1999), which help or hinder a person in maintaining good mental health. Risk and protective factors do not operate in isolation but interact (Fritz et al., 2018; Riley & Masten, 2005). For example, a person who scores high on neuroticism and has suffered from a difficult childhood is more likely to have a lower level of resilience than a person who scores high on neuroticism but had a happy childhood. Therefore, resilience should not be viewed as a static personal trait that permanently defends the lucky individual against all kinds of adversity. Instead, resilience involves complex and dynamic interactions between risk and protective factors as well as the stressors a person faces (Fritz et al., 2019; Ioannidis et al., 2020; Kalisch et al., 2019). Thus, practical and ethical challenges complicate the study of resilience: how to explore a person's response to adversity? Additionally, there are methodological challenges: How to account for the complex interactions between protective factors, risk factors, and resilience?

The multifactorial aspect of resilience (risk and protective factors are found across domains, such as biology, neuroscience, sociology, economics, and psychology; Xu & Kajikawa, 2018) illustrates the need for an interdisciplinary approach to advance the study of resilience collaboratively. A research field that is also occupied with studying resilience, and that may inspire investigations in psychology, is ecology. Environmental scientists study the resilience of ecosystems (such as lakes) by representing them as complex systems of various interacting elements (such as fish, nutrients, algae) that can end up in self-enforcing alternative stable states (such as clear or turbid water; Scheffer et al., 1993). In the lake example, the water can be clear, representing a situation in which all elements of the system thrive and maintain a healthy balance

of, among others, vegetation, fish population, and nutrients. However, this healthy balance can be disturbed (e.g., the algae in the lake grow), which leads to a causal chain of disruption (e.g., the increased number of algae limit the light at the bottom of the lake, reducing the vegetation, which, in turn, confine the fish population and nutrients, etc.) leading to a self-sustaining state of lake turbidity. The resilience of such complex systems can be studied by implementing the system in a computational model and simulating its behavior under different conditions and *perturbations* (i.e., events or stressors that disrupt the system; for example, see: Allison & Martiny, 2008; Hipsey et al., 2015; Meadows et al., 1972). In this way, one can study the resilience of lakes against different environmental conditions and perturbations, such as different climates or human interference (Scheffer & van Nes, 2007).

Especially in the case of complex systems, where the system's behavior is often better approached using non-linear equations that are hard or impossible to solve analytically, *simulation modeling* offers a solution (Taber & Timpone, 1996). Over the past decades, this approach has been extended and optimized, for example, to predict the potential effects of the climate crisis on specific ecosystems such as rainforests (e.g., Cui et al., 2021; Kumar et al., 2021). By generating testable hypotheses from the model, one can observe the accuracy of predictions and improve models and theories (Guest & Martin, 2020). As such, one can study and anticipate the resilience of complex systems scientifically.

Taking complexity models and simulation modeling to psychology offers many novel and exciting research opportunities (e.g., see: Borsboom et al., 2020; Cramer et al., 2016; Fried, 2020; Guest & Martin, 2020; Robinaugh, Haslbeck, Ryan, et al., 2021). Using computational models to simulate adverse events can help overcome practical and ethical challenges of studying resilience, as this opens the possibility to perturb models instead of people. Furthermore, complexity models may help solving the methodological challenges by focusing on the interactions between variables.

An interesting framework that developed complexity models for psychology is the network theory of psychopathology. This theory proposes that mental disorders act as complex systems and can be represented as networks of interacting symptoms (Borsboom, 2017; Borsboom & Cramer, 2013). Over the past years, the network theory gave rise to various statistical complexity models estimated from empirical data of symptom assessments (e.g., see: Epskamp, Waldorp, et al., 2018; Haslbeck & Waldorp, 2020; van Borkulo et al., 2014). Using these statistical *symptom network models,* one can estimate the direct relations between symptoms in a network structure. The models are widely used and have been applied to various mental disorders, such as MD (Cramer et al., 2016), schizophrenia (Isvoranu et al., 2017), autism (Deserno et al., 2017), and insomnia (Blanken et al., 2021).

In this dissertation, I propose a novel approach to study resilience by combining existing statistical complexity models, specifically, network models of psychopathology symptoms (Borsboom, 2017), with simulation modeling. I extend the existing statistical network models to accommodate behavior that corresponds with empirical phenomena from the resilience literature. In this way, one can model the interactions between symptoms, risk factors, and protective factors to better represent, understand and anticipate resilience. Using these network models for simulation modeling provides endless possibilities to study potential responses to adversity from different perspectives and types of data, and, thereby, progress the scientific study of resilience. As such, the work in this dissertation aims to offer a *lingua franca* to researchers from different domains (Buyalskaya et al., 2021) and novel tools to collaboratively investigate the complex concept of resilience.

In the remainder of this chapter, I further elaborate on this dissertation's approach by expanding on the network theory of psychopathology and simulation modeling in psychology. Subsequently, I discuss the current implementation of resilience research in network models together with the open questions that remain. To conclude, I outline the dissertation chapters which work on these open questions one by one.

1.2 THE PROPOSED APPROACH: COMBINING EXISTING NETWORK MODELS WITH SIMULATIONS MODELING TO STUDY RESILIENCE

1.2.1 The network theory of psychopathology and symptom models

The network theory of psychopathology proposes that mental disorders act as complex systems organized in a network of causally interacting symptoms (Borsboom, 2017; Borsboom & Cramer, 2013; Cramer et al., 2010). The network consists of *nodes* representing psychiatric symptoms and *edges* representing the direct relations between symptoms. A symptom (e.g., 'excessive worrying') can be triggered by an external event (e.g., losing one's job) and, in turn, activate neighboring symptoms as well (e.g., excessive worrying → insomnia → fatigue; Borsboom & Cramer, 2013). In this way, subsequent symptom-symptom interactions can lead to the situation in which a person is stuck in these symptom activation patterns and suffers from a mental disorder. In the first seven years since the introduction of the theory (Cramer et al., 2010), over 140 scientific papers applied the network theory of psychology empirically to various mental disorders (Contreras et al., 2019). The considerable success of the theory is due to two reasons which will be discussed below: 1) theoretically, this approach offers solutions to essential phenomena from the psychopathology literature that traditional approaches could not explain, and 2) practically, the network theory of psychopathology has been implemented in statistical models, making it possible for researchers to study mental disorders as complex systems empirically.

Traditionally, mental disorders were represented from a medical point of view, assuming the existence of an underlying mental illness that causes symptoms (Borsboom, 2017). In other words, the idea was that people suffer from a depressed mood and lack of interest *because* they are depressed. Statistically, mental disorders were represented as *latent variables*: invisible entities that act as the common cause of all the manifest (i.e., observable) symptoms (Borsboom et al., 2003). The latent variable (henceforth: LV) model is mathematically elegant: controlling for the LV in the statistical model, i.e., keeping its value constant so that it cannot act as a causal variable, makes the correlations between symptoms disappear (van Bork et al., 2019). Thus, according to the LV model, symptoms only co-occur because they stem from an underlying common cause, which is in line with the traditional and medical approach to mental disorders. In the same way that cancer symptoms disappear when a tumor is removed, mental health symptoms would vanish when a mental illness is treated (Borsboom, 2017). However, clear physical substrates that could act as a common cause of mental disorders have not been found (Borsboom et al., 2019).

Additionally, there are more aspects of mental disorders that the LV model cannot explain. The LV model views each mental disorder as a categorically distinct entity with causal power on a specific set of symptoms. From this view, it is difficult to explain the high prevalence of *comorbidity* (Cramer et al., 2010). Comorbidity refers to the situation in which a patient suffers from more than one (mental) disorder simultaneously (Angold et al., 1999). A large cohort study in the Netherlands found that 75% of patients suffering from MD also suffered from a lifetime comorbid anxiety disorder (Lamers et al., 2011). The LV model provides no explanation for the fact that two distinct entities co-occur so often. Furthermore, in the LV model, all symptoms of the same mental disorder are (statistically) exchangeable. This means that people with very different combinations of symptoms can receive the same diagnosis (Fried, 2017). In other words, the LV model offers no way to differentiate people with diverse symptomatology diagnostically. Moreover, the LV model only allows for linear relations between the disorder and symptoms, while symptoms can evolve in a non-linear fashion (Hayes et al., 2007). Some patients suddenly transition towards a much more severe state of the disorder (Hayes & Strauss, 1998). Lastly, the LV model offers no genuine, actionable interventions on the development of the disorder as symptoms are seen as merely passive indicators. From this view, intervening on symptoms does not treat the underlying mental disorder.

The network theory of psychopathology suggests solutions to all aforementioned characteristics of mental disorders. First, the theory explains comorbidity by proposing that all mental disorder symptoms can be represented in one extensive interconnected network. Symptoms that co-occur more frequently, such as the symptoms belonging to the diagnosis of MD, cluster together (Borsboom et al., 2011). Symptoms that belong to two diagnostic categories, such as 'sleep disturbances', which belongs to the MD, and

Generalized Anxiety Disorder (GAD) diagnosis, function as a *bridge symptoms* between clusters (Cramer et al., 2010). Thus, a person can develop symptoms of MD and, via a bridge symptom such as 'sleep disturbances', enter the symptom cluster of GAD. Furthermore, symptoms are not (statistically) exchangeable in the network theory, as symptoms hold causal power to their neighboring symptoms (Borsboom & Cramer, 2013). Symptoms can have no edges, weak edges, or strong edges to neighboring symptoms. Symptoms with many and strong edges have a central position in the network (Epskamp, Borsboom, et al., 2018). As such, symptoms may play different roles in developing and maintaining mental disorders (Blanken et al., 2018). Moreover, network models represent dynamic systems that may show non-linear behavior and *sudden jumps* into a severely disordered state (Borsboom, 2017). For example, network models can show *hysteresis*: the situation in which a person gets stuck in a disordered state (e.g., a depressive episode), even when the stressors that made them develop symptoms are diminished to a much lower level than what triggered symptoms. For example, solving relationship problems that triggered a depressive episode may not be enough to return to a non-depressed state (Cramer et al., 2016). Lastly, the network theory deconstructs the development of mental disorders into a causal chain of symptom activation, and in this way, offers many more targets for interventions (Blanken et al., 2019; Henry et al., 2021).

Importantly, the network theory of psychopathology has been implemented in statistical models, making it possible for researchers to empirically study mental disorders as complex systems. The statistical models can be estimated from different types of data: Gaussian data (Epskamp, Waldorp, et al., 2018), binary data (van Borkulo, Epskamp, et al., 2014), or mixed data (Haslbeck & Waldorp, 2020). Network models can be estimated on the population level from cross-sectional data or the individual level from longitudinal data (using, for example, multiple assessments per day; Bringmann et al., 2013; Epskamp, van Borkulo, et al., 2018). All network models are implemented in the freely available statistical software program *R* (see the supplementary materials of this dissertation for an introductory chapter in *R*). Together with these novel methodological tools, the network theory has caused a shift in the thinking about mental disorders, both on a theoretical and applied level (McNally, 2021).

1.2.2 Simulation modeling as a form of abductive reasoning

Using simulations and computational models to study resilience is a form of *abductive reasoning*. In abductive reasoning, one starts from empirical *phenomena* regarding a theme of interest, which are well-established general features that the scientist tries to explain (Borsboom et al., 2020; Haig, 2005). An example of an empirical phenomenon in resilience is that some people develop a mental disorder such as PTSD after facing trauma, while others do not. The researcher then starts thinking about a possible formal and mathematical model (i.e., the *theory*) that generates plausible data accommodating the phenomena. In addition, the formal model can be implemented in

a computational model to check for similarities between simulated data and empirical data that describe the phenomena. Building such a realistic, complex computational model from the ground up is not straightforward and requires a long development and evaluation process. However, one could instead estimate existing statistical complexity models from data (such as estimating a symptom network from empirical data) and, as a first approximation, adopt these estimated models as data-generating computational models. The simulations from the model can be used to 1) evaluate the model's accuracy by comparing simulated data with empirical data, 2) generate testable and specific hypotheses for empirical research, and 3) study how the model would behave under different conditions (Haslbeck et al., 2021). For example, by adjusting specific parameters of the model (e.g., decrease the probability that a specific symptom occurs) and simulating data to study how the model's behavior would change (i.e., check if overall symptomatology levels would decrease).

Combining statistical network models with simulation modeling offers many advantages. First, simulations can help researchers understand the model they estimated from data and, in that sense, be a form of data analysis (Finnemann et al., 2021). Simulations teach us what would happen according to the model, given the data (e.g., do we expect a group of remitting MD patients to end up in a depressed state again, given their symptom data?; Cramer et al., 2016). Using simulations from a formal or mathematical model can reveal patterns of behavior from the model that are difficult to anticipate when only describing the system (Robinaugh, Haslbeck, Waldorp, et al., 2021). Second, by simulating data from the estimated model, one must be explicit about the assumed dynamics that run over the network. Specifically, one must explain the rules or formulas that are used to simulate the model's behavior. By explicitly formalizing the model's dynamics, one can start scientific discussions about whether the used dynamics are plausible or the best way forward, or which improvements can be implemented. Third, one can quantify the relative importance of estimated parameters using simulations. Instead of interpreting the found relations between symptoms by looking at the network graph, which can induce subjectivity, one can quantify the relative importance of a specific parameter by changing it and seeing how the model's behavior changes.

1.3 CURRENT FINDINGS AND OPEN QUESTIONS REGARDING THE STUDY OF RESILIENCE FROM THE NETWORK APPROACH

The network theory of psychopathology and statistical symptom network models offer exciting possibilities to conceptualize the dynamical and multifactorial nature of resilience from a complex system's approach. The section below briefly discusses current findings, debates, and several open questions.

1.3.1 Assessing resilience from the estimated symptom network model's structure

The behavior of complex systems follows from their internal structure (Meadows, 2008). In other words, the way that the components of a complex system are connected determines how it will behave. Therefore, it is likely that the internal structure of a symptom network determines the course of symptom evolutions. Researchers have investigated whether the structure of estimated symptom networks, i.e., the overall strength of associations between symptoms, indeed relates to the level of symptom development over time. In a simulation study using networks of MD symptoms (Cramer et al., 2016), networks with robust connectivity (i.e., many and strong edges between symptoms) were vulnerable to developing depression. When the network was faced with stress, symptom activity spread rapidly. The network jumped towards a depressed state where it got stuck despite lowering stress levels. Networks with weak connectivity showed more gradual symptom development patterns when faced with stress and spontaneous recovery in which the present symptoms disappeared. In addition, an empirical study followed a group of patients that had suffered from MD in the past year (van Borkulo et al., 2015). Patients who relapsed into a depression after two years were characterized by symptom networks with stronger connectivity at baseline than remitting patients. These studies suggest a relationship between symptom network connectivity and resilience. However, it is not clear yet if, and how, resilience could be assessed from a baseline network's internal structure. Therefore, the first open question is how resilience could be evaluated from a network's internal structure.

1.3.2 Adding risk and protective factors to the symptom network

Researchers have suggested that the various risk and protective factors that account for resilience may be represented in a network structure (Fritz et al., 2019; Ioannidis et al., 2020; Kalisch et al., 2017, 2019; Schueler et al., 2021). The behavior of the symptom network would change due to the interactions between all these risk and protective factors and symptoms. For example, the protective factor "social support" may hinder the evolution of a depressive symptom such as "depressed mood" when faced with a stressful life experience. However, the proposed ideas have not yet been translated to a formal or computational model that can show these dynamical and multifactorial resilience characteristics. Thus, the second open question is how risk and protective factors can be integrated into symptom networks, such that they change the network's resilience.

1.3.3 Considering different timescales in the network model

Another issue is that the various risk factors, protective factors, and mental health symptoms evolve on different timescales (Bringmann et al., 2021). For example, psychopathology symptoms may evolve over days, but personality factors that are a risk factor for developing depression, such as neuroticism, may evolve over a timespan

of years (Roberts & Mroczek, 2008; Roberts & Kendler, 1999). It is not straightforward how to accommodate fast and slow-changing processes in a model. Therefore, the third open question is how to account for different timescales in such an integrated network model of resilience.

1.3.4 Studying the relation between symptom evolutions and network structure over time

Over the past years, various researchers have argued in favor of estimating individual networks instead of cross-sectional networks (e.g., see Bringmann et al., 2013; Wichers et al. 2010; Wichers et al., 2015). This is because population effects do not necessarily translate to the individual level, especially in developmental processes such as the evolution of mental disorders (Hamaker, 2012; Molenaar, 2004). Thus, to understand the relationship between network structure and the symptom development in individuals, we need to estimate individual networks. To do so, one needs longitudinal data with many repeated assessments over time (Bringmann et al., 2013; Epskamp et al., 2018). Therefore, the fourth open question is what the relationship is between the structure of network models from individual participants and their *change* in symptom evolutions over time. Additionally, in the context of resilience, a related question is what different mechanisms may account for a person's symptom evolutions, and how these evolutions are reflected in the person's symptom network.

1.3.5 Projecting the effect of interventions and perturbations on the network's symptom development

One of the most important clinical implications of the network theory of psychology is that symptoms play a different role in developing or hindering mental disorders (Borsboom & Cramer, 2013). Clinical interventions could have different propelling effects depending on the specific symptoms that are being targeted. Recent studies used simulations from network models to represent symptom-specific interventions by temporarily deactivating a symptom and calculating its effect on the rest of the network (Burger et al., 2020; Castro et al., 2019; Henry et al., 2021; Robinaugh et al., 2016). To investigate whether symptoms play different roles in developing or hindering mental disorders, we need to study the effect of both clinical interventions and stressful perturbations on the network's symptom development. The fifth and final open question is how to study the effect of different interventions on symptom evolutions.

1.4 DISSERTATION OUTLINE

This dissertation investigates the above-mentioned open questions consecutively in the following five chapters.

Chapter 2 studies how resilience could be evaluated from a network's internal structure. I integrate the concept of resilience within the network theory of psychopathology

by examining the *stability* of the *dynamics* of the projected symptom evolutions. The chapter presents the *resilience quadrant,* which organizes symptom networks based on two dimensions: 1) health versus disorder, and 2) stable versus unstable. The quadrant captures different behaviors on those dimensions: resilient trajectories despite facing adversity, and persistent symptoms despite treatment interventions. Using the example of Major Depressive Disorder, I show how different networks can show chronically depressed, relapsing, remitting, or resilient trajectories of symptom evolutions. Using simulations, a proof-of-concept shows a systematic methodology of how to investigate where in the resilience quadrant (empirically estimated) symptom networks are currently located.

Chapter 3 studies how risk and protective factors can be integrated into symptom networks, such that they change the network's resilience. The chapter proposes that symptom networks may be embedded within a web of risk and protective factors that affect the network's resilience – which depends on the symptom's expected *level* and *stability* over time. The risk and protective factors affect the symptom network's resilience by hindering or accelerating the network's symptom evolutions.

Chapter 4 investigates how to account for different timescales in such an integrated network model of resilience, with embedded symptoms, risk and protective factors. The chapter focuses on the relation between personality and psychopathology, where personality represents a slowly changing process and psychopathology a fast-changing process. Using an applied example of neuroticism and major depressive disorder, the chapter presents a system in which personality items that share content overlap with symptoms affect the symptom's tendency to be present. The chapter shows that this system generates data that accommodate important phenomena, such as the strong relation between neuroticism and depression and individual differences in the change of neuroticism levels and development of depression over time.

Chapter 5 studies how the structure of individual network models relates to their change in depressive complaints over time. Many studies have found that depressive complaints are associated with the regulation of affect. However, these studies often focus on either the population level or collect data within an intensive but brief timespan capturing relations between momentary affect and current depressive complaints. As such, neither approach captures the relation between long-term affect fluctuations and *change* of depressive complaints in individuals. This chapter investigates how affect fluctuations and evolutions of depressive complaints are associated within and across people over longer periods of time (9-14 weeks) by estimating multilevel and individual networks from a longitudinal study.

Chapter 6 studies how to investigate the projected effect of different interventions on symptom evolutions. This chapter presents a method to evaluate the effect of

symptom-specific intervention targets on the behavior of the network, which is applied to an estimated network of PTSD assessments as an empirical illustration. The method is accompanied by a newly developed R-package *nodeIdentifyR* that researchers can use to study the projected effects of targeted interventions from their datasets.

The first part of the supplementary materials includes two supplementary chapters that may support some researchers to better understand the work presented in this dissertation. The first chapter introduces *R*, the statistical program in which all studies have been conducted. The second supplementary chapter gives an overview of the network theory in Spanish to expand the theory and work into Hispanic-speaking countries and research institutions. The second part of the supplementary materials includes the supplements to Chapters 2 to 6.

2

FORMALIZING PSYCHOLOGICAL RESILIENCE FROM A COMPLEX SYSTEMS PERSPECTIVE

This chapter is under review for publication as:
Lunansky, G., van Borkulo, C. D., Blanken, T. F., Cramer, A. O. J., & Borsboom, D. (under review). Bouncing back from life's perturbations: Formalizing psychological resilience from a complex systems perspective. https://psyarxiv.com/ftx4j/

2.0 ABSTRACT

Resilience refers to the ability to return to normal psychological functioning despite facing adversity. It remains an open question how to anticipate and study resilience, due to its dynamic and multifactorial nature. This chapter presents a novel formalized simulation framework for studying resilience from a complex systems perspective. From this view, resilience is a *property* of a system that arises if a system is located in a stable and healthy state despite facing adversity. We use the network theory of psychopathology, which states that mental disorders are self-sustaining endpoints of direct symptom-symptom interactions organized in a network system. The internal structure of the network determines the most likely trajectory of symptom development. We introduce the *resilience quadrant*, which organizes the state of symptom networks on two domains: 1) healthy versus disordered, and 2) stable versus unstable. The quadrant captures different behaviors along those dimensions: resilient trajectories in the face of adversity, as well as persistent symptoms despite treatment interventions. Subsequently, we introduce a systematic methodology, using simulated perturbations, to determine where in the resilience quadrant an observed network is currently located. As such, we present a novel outlook on resilience by combining existing statistical symptom network models with simulation techniques.

2.1 INTRODUCTION

Why do some people suffer from mental illness after a disruptive, stressful life event, while others seem to bounce back relatively rapidly from such adversity without developing (lasting) psychopathology? Around 90% of people in Western countries experience at least one potentially traumatizing event during their lifetime, but the lifetime prevalence of posttraumatic stress disorder is only about 8% (de Vries & Olff, 2009; Kilpatrick et al., 2013). In the immediate aftermath of a stressful life event, depressive symptoms occur quite frequently (e.g., 25% according to Cénat & Derivois, 2014), but many initially afflicted people return to healthy physical and psychological functioning (Bonanno et al., 2004). The ability to preserve or quickly bounce back to psychological health and normal functioning after adversity is referred to as resilience (Bonanno, 2004; Kalisch et al., 2017; Werner, 1995). A meta-analysis of 54 studies that reported response trajectories of individuals after facing stress and potentially traumatic events identified different trajectory types (resilience, recovery, chronic, and delayed onset). The resilient trajectory was the most prevalent (Galatzer-Levy et al., 2018). Individuals characterized by a resilient trajectory may face mild to moderate disruptions in normal functioning (e.g., a few weeks of poor sleep and bouts of sadness), but overall maintain a stable trajectory of healthy functioning. On the contrary, a chronic trajectory is characterized by severe disruptions in functioning, which do not diminish over time without some type of intervention.

Investigating how these individual differences in resilience arise is not straightforward. The first reason for this is that resilience is a *disposition* that expresses a tendency or capacity that manifests under certain conditions or situations (Mumford, 2003). Resilience refers to a response after facing adversity, which, naturally, cannot be induced in experimental research for ethical reasons. The second reason is that the concept of resilience is complicated to analyze. Resilience is associated with many distinct variables across domains (e.g., self-compassion; MacBeth & Gumley, 2012), social support (Gariépy et al., 2016) and positive emotions (Tugade & Fredrickson, 2004) and is thus inherently *multifactorial*. There is no evidence for a set of key predictors that can explain all individual differences in resilience levels (Bonanno, 2021; Modesto-Lowe et al., 2021). Instead, resilience results from many different *protective factors* (e.g., optimism; Ellis et al., 2017) and *risk factors* (e.g., neuroticism; Roberts & Kendler, 1999) which respectively help or hinder people in maintaining or rapidly bouncing back into their normal functioning (Fritz et al., 2018; Xu & Kajikawa, 2018). Importantly, these risk and protective factors do not operate in isolation but interact with one another (Ellis et al., 2017; Gijzel et al., 2019; Riley & Masten, 2005; Weinans et al., 2021). For example, two people with a similar level of neuroticism can still have different responses to stressful events, such as losing their job. A person who scores high on neuroticism and also has suffered from a difficult childhood is more likely to have a lower level of resilience than a person who also scores high on neuroticism but had a happy

childhood. A further element that makes the study of resilience complicated is its *dynamic nature* by which someone is successfully (or not) adapting to its environment and various stressors over time (Shafi et al., 2020; Crameri et al., 2021; Hill et al., 2018; Kalisch et al., 2017; Rutter, 2012; Sapienza & Masten, 2011; Stainton et al., 2019). Instead of representing resilience as a static trait that permanently shields someone from all types of misery, evidence suggests that resilience levels within individuals can change over time (Infurna, 2021; Stainton et al., 2019). Thus, resilience involves complex and dynamic interactions between risk and protective factors as well as the stressors a person faces, which current accounts of resilience fail to accommodate (Kalisch et al., 2019).

The network theory of psychopathology offers a theory and modeling framework that allows taking the multifactorial and dynamic nature of resilience into account (Borsboom 2017; Kalisch et al., 2019). The central idea of this theory is that mental disorders act as *complex systems* (Borsboom, 2017; Borsboom & Cramer, 2013). Complex systems consist of interacting elements that produce a pattern of behavior (Meadows, 2008). The take-away message from the complex systems approach is that a system's behavior follows from its internal structure. To study the system's behavior, one should understand how the whole system operates instead of studying every variable or component in isolation. The internal structure of the system can lead to a *self-sustaining state*, meaning that the system gets 'stuck' in a certain state that is difficult to break (Scheffer et al., 1993). The network theory of psychopathology proposes that a mental disorder is such a self-sustaining state, ultimately caused by direct symptom-symptoms interactions (Borsboom, 2017). Symptoms are organized in a network and directly affect each other: for example, insomnia causes fatigue, which, in turn, results in concentration problems (Borsboom & Cramer, 2013). The concentration problems might trigger a depressed mood, which, over time, results in feelings of worthlessness. The end result of these symptom-symptom interactions (i.e., insomnia ▸ fatigue ▸ concentration problems ▸ depressed mood ▸ feelings of worthlessness) is a depressive episode (Borsboom, 2017). The number of active symptoms defines the *state* of the symptom network. One may use DSM diagnostic cut-offs to determine the number of symptoms that depict the network's state: 1) relatively few symptoms active (below a diagnostic cut-off), a *healthy state*; or 2) relatively many symptoms active (above a diagnostic cut-off), a *disordered state*.

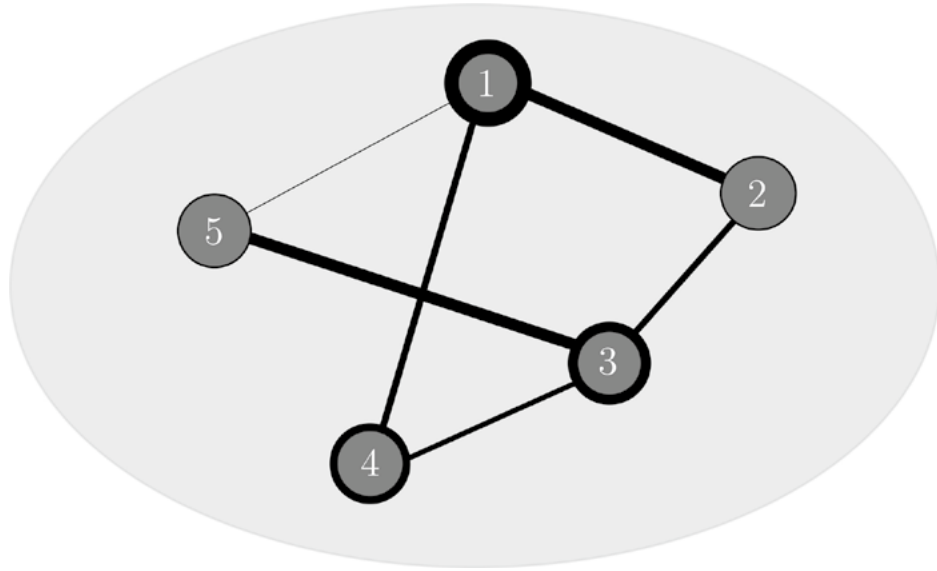

Figure 2.1. An example of a symptom network model. The *nodes* in the network (the circles in the figure) represent symptoms, such as 'insomnia' or 'depressed mood'. The node parameters (illustrated by the node borders) are called *thresholds* and express the preference of a symptom to be present. Strong thresholds (shown by thick borders) indicate a symptom's large preference to be absent, meaning that the symptom is less likely to activate. Contrary, weak thresholds (thin borders) indicate that a symptom has a minor preference to be absent and can become present more easily. The *edges* in the network (the lines between the nodes in the figure) represent the association between the symptoms. The stronger the association (thicker lines), the stronger the preference of symptoms to be in the same state. Thus, when one symptom is present, a strongly connected neighboring node is more likely to become present as well.

The most likely behavior of the symptom network is determined by its *architecture* (i.e., the internal structure). The network's architecture consists of 1) the *connections* between the symptoms and 2) the *thresholds* of each symptom to become active. Strongly connected symptoms are more likely to activate each other (Cramer et al., 2016). For example, suppose the depressive symptom 'insomnia' is strongly connected to 'excessive worrying'. In that case, the presence of insomnia increases the likelihood that excessive worry will activate as well, and vice versa. In this way, symptom networks with weak connectivity are more likely to become stuck in a vicious cycle of symptom-symptom interactions (van Borkulo et al., 2015). In addition, each symptom has a threshold for activation. Symptoms with *low* thresholds (e.g., insomnia) are more easily activated when faced with some perturbation (e.g., a stressful event) than symptoms with *high* thresholds (e.g., suicidal ideation; Schweren et al., 2018). In this way, individual differences in the development of psychopathology could potentially be explained by differences in the network architecture across people.

However, it remains an open question how to study the resilience of networks, specifically, what type of outcome should be used to define whether a network is resilient. It is currently unknown how the network's architecture relates to resilience. To answer that question, one needs to study how the symptom network's behavior is affected by adversity. One can expose the symptom network to perturbations by simulating data under different conditions that represent adversity. In this way, it is possible to investigate how the network's behavior would evolve according to the model. Alternatively, one can explore how a specific symptom network would respond to treatment interventions after getting stuck in a disorder state. By simulating data under the situation that a network receives treatment interventions, one can study how susceptible a depressed network is to change. In other words, one can investigate the *stability* of the network's state against simulated perturbations that represent stressors or treatment interventions. Thus, by using simulations, we can study how resilient a network is against adversity (i.e., the stability of a healthy state) and how easily a network will respond to treatment interventions (i.e., the stability of the disorder state). As such, one can generate clear, testable, and specific hypotheses on what factors contribute to the system's resilience that can be used for empirical validation.

This chapter will show how to study resilience using a statistical network model of psychopathology combined with simulations. The chapter is set up as follows. Section 2.2 ("The resilience quadrant") introduces the *resilience quadrant*, which organizes symptom networks based on their most likely state (healthy or disordered) and stability against perturbations. We show that the quadrant captures different behaviors along those dimensions: resilient trajectories in the face of adversity, as well as persistent symptoms despite treatment interventions. Section 2.3 ("Proof-of-concept") shows how to study in which regime of the quadrant symptom networks are currently located using simulations with exemplary architectures. Section 2.4 ("Discussion') concludes with the necessary steps to further the study of resilience from a complex systems approach, such as implementing risk and protective factors to symptom networks.

2.2 THE RESILIENCE QUADRANT

We present the resilience quadrant as a formalized simulation framework that shows the four different resilience regimes in which a symptom network can be located (see Figure 2.2). The framework is formalized because it explains how different network architectures lead to differences in resilience and how we could study the resilience of networks. The quadrant organizes networks by two dimensions: the network's *projected state* (state-axis) and the *stability* of that state (stability-axis). The state-axis denotes whether the system can be expected to be in a healthy or disorder state, given the network's architecture. The stability axis indicates how susceptible the projected state is to change when faced with perturbations. Using the example of

Major Depressive Disorder (MDD), a network of depression symptoms can be located in a resilient, remitting, relapsing, or chronically depressed regime of the quadrant.

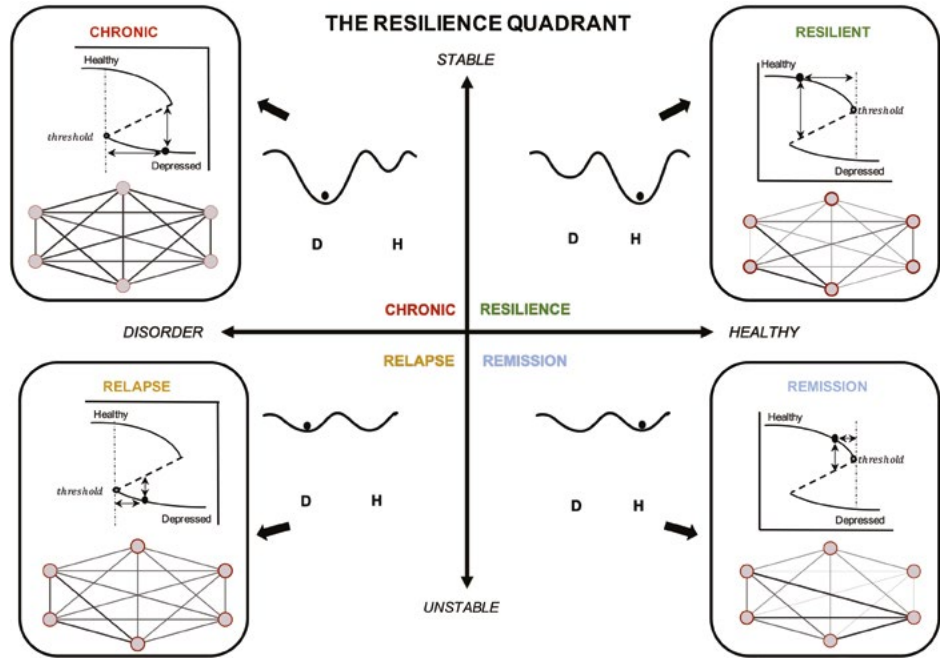

Figure 2.2. The resilience quadrant. The center shows the resilience quadrant of a (simplified) mental health system with two alternative stable states: healthy and depressed. The valleys in each quadrant represent the underlying attractor landscape for the two alternative states. For example, in the "resilient" regime, the system is located within the deep, steep, and wide attractor basin of the healthy state, and therefore unlikely to fall into the shallow attractor basin of the depressed state, even in the face of adversity. The corresponding boxes show the current location in the system's trajectory, where the upper trajectory represents the healthy state and the lower trajectory the depressed state. The switch from one state to the other is called a *sudden jump*, which can also be represented by shifting from one attractor basin into another. Within each box, corresponding network architectures are shown. Nodes represent depression symptoms, and edges represent associations (e.g., logistic regression coefficients) between symptoms, while the thickness of edges represents the strength of this relationship. The thickness of red borders around nodes represents the magnitude of threshold parameters, which differ per node.

A visual metaphor that can explain the discussed link between the stability of the network's state and resilience is the ball-in-a-cup metaphor (see Figure 2.3, which is often used in dynamical systems theory; e.g., see Scheffer et al., 2018). The cup represents the *attractor basin* of the network, which corresponds to the state the network is gravitating towards. As introduced above, the states are simplified to two options: a healthy state with few active symptoms and a disordered state with many

active symptoms. The ball represents the system's current state, which can take on all possible combinations of active and inactive symptoms. The steepness and width of the cup represent how stable the ball lies in the attractor. If the attractor basin is broad, deep, and steep, the ball is likely to stay at the lowest point and unlikely to move and be pushed over the edge. In contrast, an attractor basin that is narrow, shallow, and flat is unstable since the ball is likely to roll out of the attractor basin (Holling, 1973). The ball can be pushed by perturbations, such as minor daily stressors or adverse life events (e.g., divorce or the death of a loved one; Fried et al., 2015). However, the external events may also represent alleviating interventions, such as clinical treatments that aim to move a patient towards a healthy state. The influence of the perturbation on the ball's behavior depends on the force pushing the ball forwards (i.e., how strong the perturbation itself is) and the form of the cup (i.e., how deep and steep the attractor is). Together, these determine the probability that the ball will switch from one state to another. Thus, a network situated in a healthy and stable attractor, with an unstable attractor for the disordered state, will show a resilient trajectory. This means that resilience is no longer a specific component of the network (e.g., a variable in the network or a particular set of factors) but a *property* of the network.

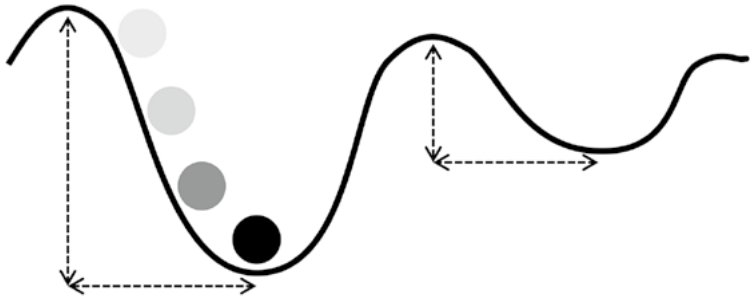

Figure 2.3. The ball-in-a-cup metaphor. The depth and width of the attractor determine how easily an imaginary ball falls into and out of the attractor, and thus, how stable the system is currently located in the attractor. The left basin is stable, represented by its wide and steep valley. Contrary, the right basin is unstable due to its shallow and narrow form.

In the resilient regime (the upper-right area of Figure 2.2), the network is located in a healthy and stable state. This means that the network's small number of active symptoms is stable in the face of adversity. Some symptoms may be triggered after an event, but these will show spontaneous recovery. Networks with weak connectivity and high thresholds will be located in this regime. The healthy state can also be unstable in which symptoms are more easily activated after facing perturbations, which is depicted in the lower-right regime ("remitting") of the quadrant (see Figure 2.2). For example, patients in remission may be characterized by an unstable healthy state and thus not resilient even though their profile and number of depression symptoms might fall below the clinical cut-off for diagnosis. Networks with slightly

stronger connectivity but lower thresholds than the resilient network are located in the remitting regime. The left part of the quadrant depicts the unhealthy state of the network, whereas the upper left shows the chronic depression regime. A network in this regime is stuck in an unhealthy stable state and therefore unresponsive to clinical interventions. Patients who suffer from chronic depression can be hypothesized to fit this category, as they are often not responsive to many (first) treatment interventions (Fava, 2003; Hölzel et al., 2011). Networks with strong connectivity and low thresholds will be located in this regime. Disordered symptom networks can also be unstable, representing, for example, groups of patients that are relapsing into depressive states (shown in the bottom-left regime of the quadrant). The relapsing networks also have strong connectivity and low thresholds, but these parameters are less extreme than in the chronically depressed network.

We use simulations to study where in the quadrant a network is located in two steps. First, we check the location of the network on the state-axis (i.e., the projected state of the network): healthy versus disordered. To study the projected state of the network, we simulate many observations[1] from the network. We calculate the mean number of active symptoms, representing the most likely state in which the network will end up. Second, we study the location of the network on the stability-axis: stable versus unstable. We investigate the stability of the projected state simulating perturbations to the network. Note that different perturbations are needed to examine the stability of a healthy or disordered projected state. To study the stability of a healthy projected state, we apply *aggravating interventions* mirroring the development of depressive symptoms due to an adverse life event. Aggravating interventions temporarily increase the level of symptoms in the simulations. To the contrary, we apply *alleviating interventions* to investigate whether a disordered projected state is susceptible to change. Alleviating interventions represent treatment interventions by forcing symptoms to be inactive at specific moments of the simulation. In the following section, we provide a proof-of-concept of how we can assess in which regime of the resilience quadrant symptom networks are currently located.

2.3 PROOF-OF-CONCEPT

In the current section, we explain how to identify typical cases of networks for every regime in the resilience quadrant. We constructed four different networks to show resilient, remitting, relapsing, or chronically depressed trajectories. We constructed these networks by altering the architecture (i.e., threshold and connectivity

1 For specific types of network models, the most likely state of a network can also be calculated analytically. For example, the most likely state of the model used in this chapter (the Ising model) can be solved analytically for networks up to ten nodes using the R-package *IsingSampler* (Epskamp, 2020). However, as we also simulate perturbations to check the stability of the most likely state, we use the same type of simulations to position the network on both the state- and stability-axis.

parameters) of an empirically estimated baseline symptom network in four ways (see Figure 2.4). The baseline symptom network represents nine depression symptoms in a population with healthy and depressed participants. The four networks differ in their architecture, specifically their connectivity and thresholds, and were constructed to mimic characteristic behavior for each quadrant in Figure 2.2. To construct the network in the resilient regime, we decreased the connectivity and made the thresholds higher (i.e., the symptoms will be less likely to activate), which will make the healthy state of the network more stable. We did the opposite for the network located in the chronically depressed regime by increasing the connectivity and making the thresholds lower (i.e., making the symptoms more likely to activate). We made the network's projected states more unstable for the remitting and relapsing networks by altering the connectivity and threshold parameters in opposite directions (see the supplementary materials for a detailed description of how we constructed the networks).

All analysis code and research materials are available at https://osf.io/gv46e/. Analyses were done with R, version 4.1.2 (R Core Team, 2021) and the packages *IsingFit*, version 0.3.1 (van Borkulo et al., 2014), *qgraph*, version 1.9 (Epskamp et al., 2012), *ggplot2*, version 3.3.5 (Wickham, 2016), *tidyverse*, version 1.3.1 (Wickham et al., 2019) and *ggpubr*, version 0.4.0 (Kassambara & Kassambara, 2020). This study's design and its analysis were not pre-registered.

2.3.1 Health versus disorder: Simulating observations without perturbations

The first dimension in the resilience quadrant is health versus disorder. To assess whether a system characteristically displays healthy or disorder patterns, one can evaluate whether the expected number of active symptoms exceeds a clinical cut-off. For instance, in the present case, we simulated data from the four networks to show that these specific networks end up in different projected states (healthy or depressed). The supplementary materials to this chapter explain the simulation technique used to simulate the observations from the networks in detail. The simulated observations can be seen as 'repeated measures' of the nine depression symptoms for the same fictitious population of participants that each network represents. In that way, the simulated observations approximate the most likely symptom developments of every network, given the network's architecture. We calculated the projected state of every network by taking the mean of the sum scores of active symptoms over all simulated observations.

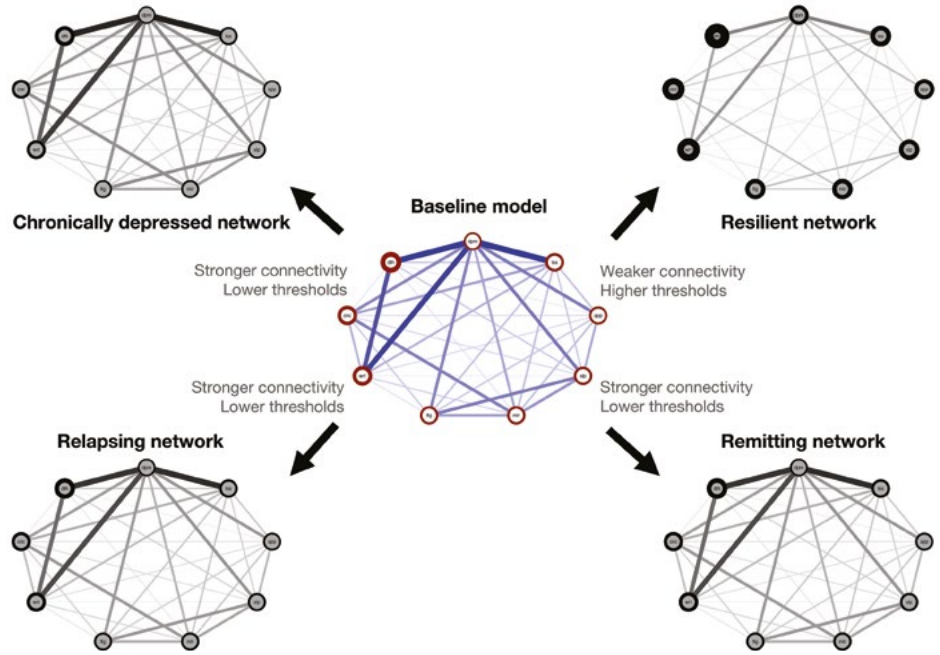

Figure 2.4. Constructing resilient, relapsing, remitting, and chronically depressed network models. We create four networks that show resilient, remitting, relapsing, and chronically depressed trajectories by manipulating an empirical baseline network model (in the centre). The four networks are created by multiplying the connectivity and threshold parameters of the baseline model's architecture, and in this way, increasing or decreasing the parameters. The four constructed networks show behavior that fits the four regimes of the resilience quadrant. The thickness of edges represents the magnitude of the connectivity, and the thickness of node borders represents the strength of the thresholds. As can be seen from the figure, the relapsing and remitting networks have quite similar architectures. See the supplementary materials for the exact values with which the baseline model parameters are multiplied to construct the four novel models. Abbreviations of the nodes refer to depression symptoms as follows: dpm = depressed mood, lss = loss of interest, app = appetite disturbance, slp = sleep disturbance, mtr = psychomotor agitation, ftg = fatigue, wrt = feelings of worthlessness, cnc = concentration problems, and dth = thoughts of death.

The mean sum score falls below or above a specific clinical cut-off value for diagnosis. The clinical cut-off value used in these simulations is the (simplified[2]) clinical cut-off value for diagnosing MDD, namely a sum score of five or more active symptoms denoting a depressed state and less than five active symptoms indicating a healthy state.

2 The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013) states that for a diagnosis of MDD, 5 symptoms should be present, of which 'loss of interest' or 'depressed mood' should be present (American Psychiatric Association, 2013). For simplicity, here we do not consider which specific symptoms are present.

Table 2.1 and Figure 2.6 show the results from the simulations. The projected state for the *resilient network* is healthy since the mean sum score of simulated observations falls below the cut-off of 5 symptoms (mean = 0.03, sd=0.19). The *remitting network* showed more fluctuations. There is no clear state for this model and the number of active symptoms switched from a few active symptoms to a state with a high number of active symptoms. However, based on the mean of the active symptoms (mean = 3.83, sd = 3.95) the projected state of the networks falls below the cut-off value of five or more active symptoms. It is therefore located within the healthy regime of the resilience quadrant. The *relapsing network* showed some fluctuating symptom evolutions but with more active symptoms. The mean sum score of the relapsing network falls above the cut-off value (mean = 8.36, sd=0.87), and its projected state is therefore depressed. The *chronically depressed network* model showed many active symptoms (mean = 8.87, sd=0.47), and its projected state is consequently depressed.

2.3.2 Stability versus instability: Simulating observations with perturbations

After evaluating whether the characteristic behavior exhibits healthy or disorder states, we assessed the second domain of the resilience quadrant: stability versus instability. To this end, we perturbed the networks to study how stable their projected state is. We applied aggravating interventions to networks with a healthy projected state by activating all symptoms for specific moments in the simulation. We applied alleviating interventions for networks with a projected disordered state by forcing all symptoms to be inactive at particular moments. Figure 2.5 gives an example of simulated aggravating interventions, and the supplementary materials of this chapter explain the simulations in detail. After the interventions, the simulation of observations continued in its regular fashion. The network's architecture determines whether the following simulated observations can get 'stuck' in the presence of symptoms or maintain a low level of symptoms. We calculated the effect of the interventions by computing the mean of the active symptoms over all observations. This symptom mean can again fall above or below the chosen clinical cut-off value, determining whether the system's projected state after facing aggravating or alleviating interventions remains healthy or depressed.

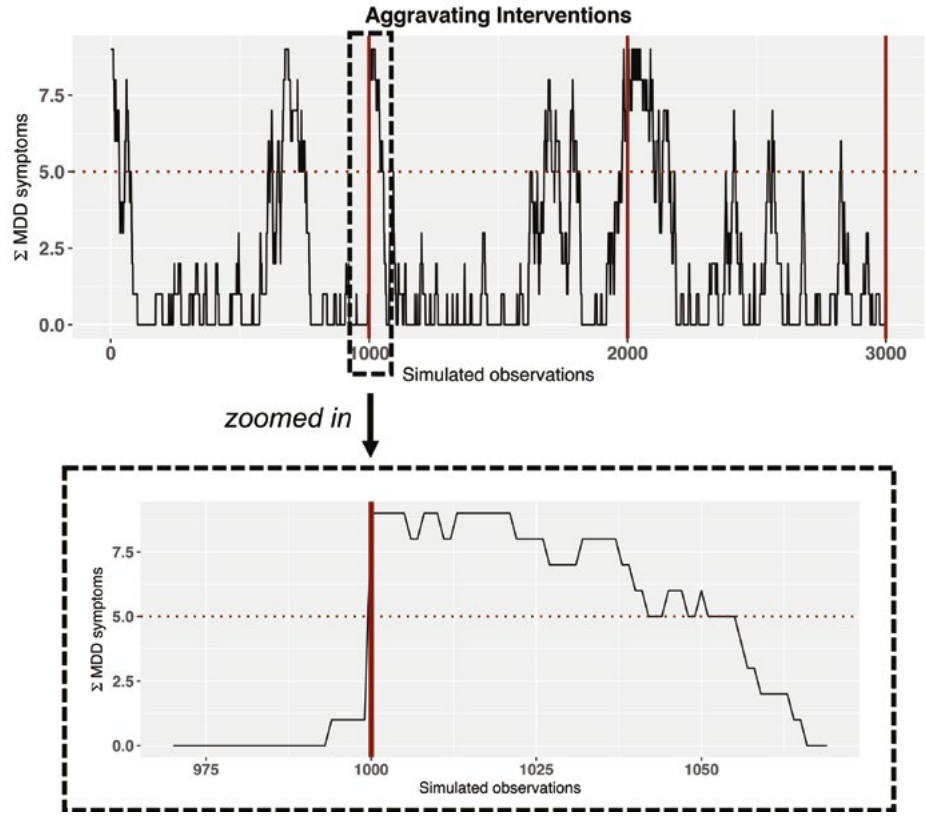

Figure 2.5 An example of simulated aggravating interventions. Simulations are based on the estimated baseline depression model (see the supplementary materials). The x-axis represents the simulated observations, the y-axis the sum scores of the active depression symptoms. The red vertical lines represent every moment an aggravating intervention is simulated, meaning that all symptoms are forced to be active for one moment in the simulation. The dashed red line denotes the (simplified) clinical cut-off value for diagnosing MDD, namely a sum score of five active symptoms. The lower figure zoomed in on one intervention to show how the system recovers in detail. In this plot, the network with these estimated parameters generating these dynamics will fall below the clinical cut-off value for diagnosing depression most of the time.

Based on the previous results, we simulated aggravating perturbations for the networks projected to be in the healthy state and alleviating interventions for the networks projected to be in the unhealthy state (See Table 2.1 and Figure 2.6). The *resilient network* bounced back very quickly from every aggravating intervention and remained in a healthy state with almost no actively present symptoms (mean = 0.19, sd = 0.85). Interventions had more effect on the *remitting network*, in which the state of the network sometimes reached a depressed state. However, symptom evolution patterns were still highly fluctuating. The mean sum score of the network now falls above the cut-off (mean = 5.76, sd = 3.65). In the *relapsing network*, the applied

alleviating interventions successfully diminished the number of symptoms but with high fluctuations (mean = 4.13, sd = 4.1). The *chronically depressed network* model remained depressed most of the time despite alleviating interventions. However, the alleviating interventions seem to have some effect as symptom presence fluctuated (mean = 7.41, sd = 3.22).

Table 2.1. The mean and standard deviations of the simulated dynamics with and without perturbations for every constructed network.

Symptom Sum Score	Constructed Symptom Networks							
	Resilient		Remitting		Relapsing		Chronically depressed	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Without perturbations	0.04	0.19	3.83	3.95	8.36	0.87	8.87	0.47
With perturbations	0.19	0.85	5.76	3.65	4.13	4.1	7.41	3.22

2.3.3 Determining the position of the networks in the resilience quadrant

We can evaluate where the networks are located in the resilience quadrant by comparing the previous results. First, we assessed the networks on the health versus disorder domain to locate them on the left or right side of the state-axis in the quadrant (See Figure 2.2). If the network's projected regime fell below (above) the clinical cut-off, we positioned the network on the healthy (depressed) domain in the right (left) side of the quadrant. Second, we evaluated the networks on the stable versus unstable domain to locate them on the upper or lower side of the stability-axis in the quadrant. If the network's projected state after perturbations remained the same as the state without perturbations (i.e., the mean sum score of active symptoms still fell below or above the clinical cut-off; healthy or depressed), we positioned the network on the stable regime on the upper side of the quadrant. Otherwise, we located it in the unstable regime on the lower side of the quadrant.

Figure 2.6 shows the results of all the simulations for the four networks. The *resilient network* showed a healthy state, which was stable against aggravating interventions and is therefore located in the "resilient" regime of the resilience quadrant. The *remitting network* showed unstable dynamics, with a symptom mean score below the cut-off, but which jumped towards an unhealthy state after aggravating interventions. Therefore, the remitting network is located in the unstable healthy ("remission") regime. The *relapsing network* is projected to be in an unstable depressed state, which can jump to a healthy state after alleviating interventions and is therefore placed in the "relapsing" regime of the quadrant. The *chronically depressed network* remained depressed despite alleviating interventions and is thus situated in the stable depressed ("chronically depressed") regime.

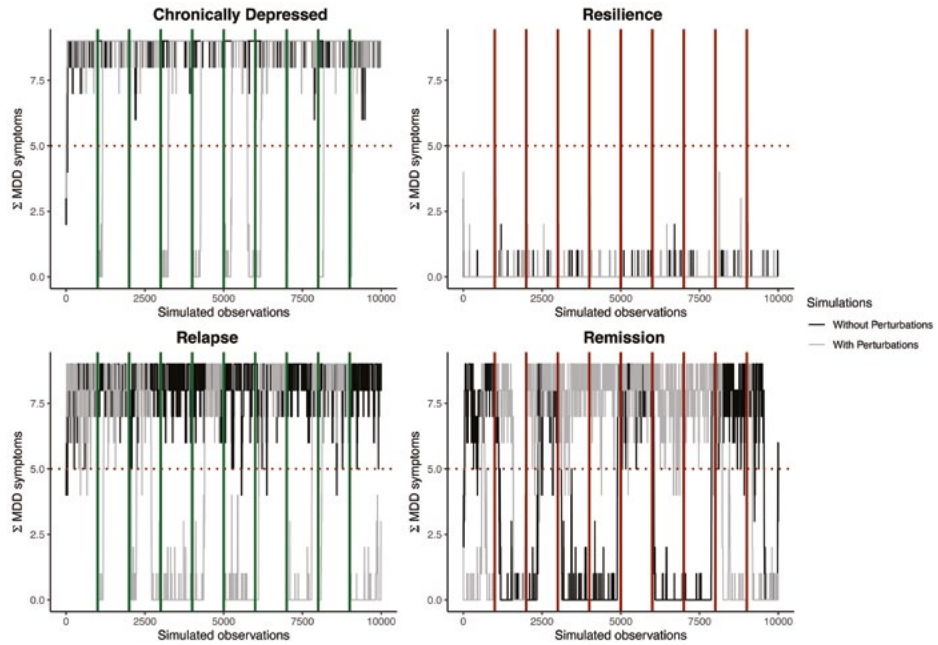

Figure 2.6. The projected symptom evolutions for four networks in distinct regimes of the resilience quadrant. The x-axis of every plot shows the simulated observations, and the y-axis the sum of the present symptoms, where a higher score indicates a higher level of depression. The dashed horizontal red line indicates the clinical cut-off value of 5 symptoms or more for a diagnosis of MDD. The vertical lines indicate the moments where interventions are simulated, where red lines indicate aggravating interventions (all symptoms are forced to be present), and green lines indicate alleviating interventions (all symptoms are forced to be absent). The upper-right plot shows the symptom evolutions for the symptom network located in the resilient regime. Despite aggravating interventions, it displays a healthy and stable state, which follows from the projected low number of present symptoms. The lower-right panel shows the results for the network that was constructed to show an unstable healthy state located in the remitting regime of the quadrant. The projected state of the network is healthy, but it is heavily affected by the aggravating interventions. The lower-left panel shows the projected evolutions of the network located in the relapsing regime, which is characterized by an unstable depressed state that recovers from alleviating interventions. The upper-left panel shows the results for the network located in the chronically depressed regime, which is characterized by high levels of symptomatology despite alleviating interventions. The chronically depressed network is therefore unlikely to be susceptible to treatment interventions.

2.3.4 The relation between network architecture and resilience

The networks in the four quadrants were constructed from a baseline estimated network. We arrived at the typical networks by systematically altering the parameters of the baseline network. This process is represented in Figure 2.4. As is shown in the figure, a *chronically depressed network* arises when interactions between symptoms are strong (stronger connectivity), and the tendency of each symptom to be active is stronger (lower thresholds). Thus, both stronger interactions with other symptoms and

the degree to which symptoms have an autonomous tendency to be active contribute to a loss of resilience. In contrast, the *resilient network* is a perfect mirror of the chronically depressed network: it features weaker symptom-symptom interactions and a more favorable threshold of the individual nodes. Notably, the *relapsing* and *remitting networks* are located in the parameter space in between the chronically depressed and resilient networks. They have slightly less favourable thresholds and somewhat stronger connectivity. In this area of the parameter space, simulations suggest that many (nearly) equivalent models can be constructed through slight changes in the model parameters. This indicates that to assess resilience, the threshold parameters of the model cannot be ignored, as lower thresholds can offset stronger interactions and vice versa. In addition, observe that small changes in the model's parameters suffice to alter their position in the resilience quadrant. We return to the implications of these results in the discussion.

2.4 DISCUSSION

This chapter proposed a novel framework to formalize and study resilience using a complex systems approach to psychopathology. Specifically, we combined (estimated) symptom network models with simulations to study how resilient a symptom network is based on its architecture. We have introduced a systematic methodology to determine where a given network is located in the resilience quadrant, which operates in two steps. First, assess whether the system characteristically exhibits symptom activation beyond the clinical cut-off. Second, evaluate whether the system state is robust against perturbations using simulations (where these are either aggravating or alleviating depending on the characteristic state of the system). Applying this analysis to a baseline symptom network of depression, an expected finding is that stronger connectivity and less favorable thresholds together can make a network chronically depressed. However, two important additional findings emerged. First, the effects of changes in thresholds and connections can offset each other (see also Kruis, 2021). This finding is important to incorporate in research. It implies that empirical tests, such as those based on the Network Comparison Test (van Borkulo et al., 2022) which compares networks based on only their connectivity, should not be confused with tests of resilience. This is because two networks with equal connectivity but different thresholds may show different levels of resilience. Second, the differences in parameter values that result in different quadrants are slight. This potentially explains why resilience is thought to be dependent on complex configurations of factors thought to support resilience, in which many factors interact and have relatively weak connections to each other.

It is our hope that thinking about and studying resilience from a complex systems approach will ultimately lead to novel methods that can improve the assessment and prediction of response trajectories to adverse events or treatment efficacy. For

example, to help decide what the network structure of a patient may look like and, as such, help decide in which regime of the resilience quadrant patients could be located. This may contribute in determining optimal intervention strategies, as patients with unstable network structures may need less strong treatment interventions compared with patients with chronically depressed networks. In the remaining section, we will outline the most critical steps that, in our view, will help advance the research program of resilience from a complex systems approach in psychology.

2.4.1 Extend the ideas presented in this chapter to other statistical network models

The network model that was used in our simulations (see the supplementary materials for details) is helpful for theoretical exercises since it is a relatively simple model that can accommodate various complex phenomena aligning with mental disorders, such as phase transitions from healthy to depressed states (Finnemann et al., 2021). However, the model used in this chapter originates in physics and is designed to explain ferromagnetism (Ising, 1925; see the supplementary materials). The model is potentially too simplified to be a realistic representation of the dynamic course of symptom development. For example, symptoms can only be active or inactive in the model, and the associations between symptoms cannot change over time. The ideas outlined in this chapter could be extended to other models, which are more useful to represent the course of depressive complaints or resilient responses. The Gaussian Graphical Model (GGM; Epskamp et al., 2018) allows for continuous and ordinal data, such as symptoms measured on a Likert-scale. The Mixed Graphical Model (MGM; Haslbeck & Waldorp, 2020) is a network model that can be estimated from both continuous and categorical data and is thus a suitable candidate to study the relationships between symptoms and various types of risk or protective factors. Vector Auto-Regressive models (VAR models; Bringmann et al., 2013) can be used to study the relationships of variables over time (e.g., see Henry et al., 2021), such as daily fluctuations of moods and affect states (e.g., see: Snippe et al., 2017; Wichers et al., 2015). One could also add interventions to continuous time VAR models (Ryan & Hamaker, 2021). Ideally, models would also be built from the ground up to allow for specific time-varying elements of resilience (Robinaugh et al., 2020), such as the computational model for Panic Disorder (Robinaugh et al., 2021).

2.4.2 Expand the modeling of perturbations

This chapter proposed a way to represent and study the resilience of symptom networks as an outcome by comparing simulated dynamics before and after alleviating or aggravating interventions. Perturbations could be extended such that they represent different types of adversity or treatment interventions in life. Instead of representing interventions as (de)activating all symptoms at specific moments, one could also model interventions that represent chronic stressors, minor daily hassles or permanent treatments (i.e., taking medication that permanently impacts

symptom development). One could, for example, (de)activate specific symptoms for the duration of the simulations. In addition, one could target specific symptoms for alleviating or aggravating interventions to investigate which symptom is projected to have the largest influence on the resilience level of the network (see Chapter 6 of this dissertation). Alternatively, one could target a random number of symptoms for every intervention, realistically representing stressful life events or treatment interventions.

2.4.3 Include risk and protective factors to symptom networks

Resilience results from various risk and protective factors across domains (Fritz et al., 2018; Xu & Kajikawa, 2018). This chapter assessed resilience from a symptom network architecture by studying the stability of symptom evolutions after facing perturbations. Symptom networks could also be extended with risk and protective factors that help or hinder the further development of symptoms. These risk and protective factors may directly affect the symptom network's architecture such that it becomes more or less resilient (See Figure 2.7) (Isvoranu et al., 2017; Kalisch et al., 2019; Chapter 3 of this dissertation). For example, the risk factor of being sexually abused in childhood is directly linked to the development of feelings of guilt later in life (Isvoranu et al., 2017), while the protective factor 'social support' may hinder the evolution of 'depressed mood' (e.g., Gariépy et al., 2016). Risk (or protective) factors may directly influence the development of symptoms and strengthen (or weaken) their connections or thresholds. Networks targeted by many risk factors may have stronger connections between symptoms, making them more vulnerable to stressful events. In these networks, stressors could lead to vicious cycles of persistent symptom activation resulting in full-blown depressive episodes in which the network gets stuck (Cramer et al., 2016).

One could study whether groups of people that score high on certain risk or protective factors have, indeed, a different symptom network structure. This could be achieved by estimating a network from both symptom data and risk and protective factors (using, for example, the MGM network model for mixed data; Haslbeck & Waldorp, 2020). Afterward, one may condition on specific values of the risk and protective factors, such as the presence of protective factors and the absence of risk factors, to obtain the symptom network structure for the people represented by that situation. One could feed that symptom network into the proposed framework in this chapter by simulating data and perturbations from the specific symptom network architecture. In this way, one could study whether specific risk and protective factors lead to differences in resilience from a complexity approach. However, the problem is that the simulation techniques presented in this chapter currently only work for binary data. Future research could apply the proposed logic to networks estimated from different data, such as mixed data (i.e., symptoms and risk or protective factors measured on different scales).

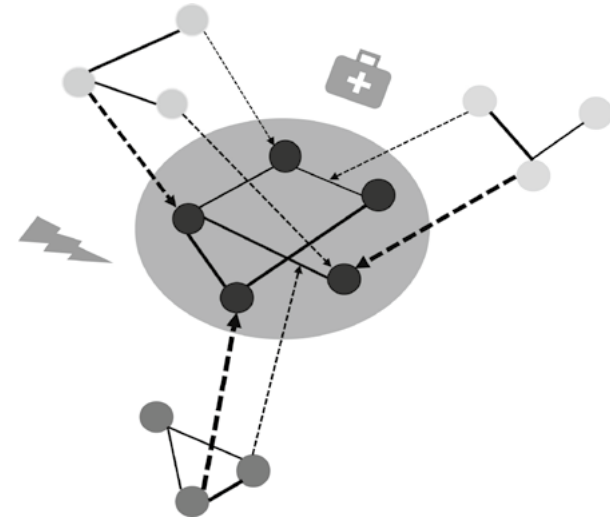

Figure 2.7. Representation of a symptom network with risk and protective factors. A representation of a symptom network model (the black nodes represent symptoms), where symptoms are related to other factors from distinct domains (the nodes in grey tones; e.g., personality, social factors, biological factors). These external factors can act as protective factors by lowering the possibility that symptoms occur, or as risk factors by increasing the likelihood that symptoms will develop. Relations between all variables in the model may vary in strength (shown by the thickness of the lines). In addition, external perturbations (aggravating interventions; the lightning bolts, and alleviating interventions; the medical case) may also influence the symptom-symptom interactions. Protective factors, such as relationship quality or partnership satisfaction, may dampen the interactions between symptoms. When a person starts feeling worried, their spouse can decrease the probability that worrying will lead to other symptoms by offering social support (Røsand et al., 2012). (The figure is an adaptation of Figure 3.1 in Chapter 3).

2.4.4 Work on a personalized framework of resilience assessment and prediction

Our presented framework may be helpful to generate hypotheses on network models of different participant groups, such as comparing clinically depressed patients with healthy individuals. One could compare the networks of groups of people that did and did not develop mental disorders over time (van Borkulo et al., 2015). Using our proposed framework, an exciting possibility is to investigate whether differences between these groups could already be detected at baseline. However, this does not mean that we can predict response trajectories or assess the resilience of every individual from these groups. One of the biggest challenges for formalizing psychological phenomena such as mental health is the heterogeneity of people (Molenaar, 2004). Heterogeneity implies that trajectories at the group-level do not directly translate to every individual (Hamaker, 2012). To personalize a formal framework of resilience, our proposed framework needs to be adapted to individual models. A recent example of a study in this direction suggests monitoring individuals over time on stressor exposure

and mental health problems (Kalisch et al., 2021). Deviations of the individuals from a 'normative' trajectory (for example, based on the mean of the studied sample of participants) could be detected early and related to later outcomes. Another example is to combine intensive data collection of daily momentary moods and stressful events with periodic assessments of symptom evolutions (Kuranova et al., 2020). In this way, one could study if the recovery from adverse events, in terms of maintaining positive momentary moods, could be related to an increase in symptom development or resilient responses.

2.4.5 Concluding

Resilience is an inherently multifactorial and dynamic concept. As such, we have to understand how different mechanisms work together to make a person cope, thrive, or break apart after facing hardship (Ioannidis et al., 2020; Kalisch et al., 2017). This chapter presented a novel way to study resilience from a complex system's perspective in psychology by combining existing statistical symptom network models with simulation techniques. We hope that the general framework will aid future researchers from different domains to advance the study of resilience collaboratively.

3

INTEGRATING RISK AND PROTECTIVE FACTORS TO PSYCHOPATHOLOGY NETWORKS

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3.0 ABSTRACT

Inspired by modeling approaches from the ecosystems literature, in this chapter, we expand the network approach to psychopathology with risk and protective factors to arrive at an integrated analysis of resilience. We take a complexity approach to investigate the multifactorial nature of resilience and present a system in which a network of interacting psychiatric symptoms is targeted by risk and protective factors. These risk and protective factors influence symptom development patterns and thereby increase or decrease the probability that the symptom network is pulled towards a healthy or disorder state. In this way, risk and protective factors influence the resilience of the network. We take a step forward in formalizing the proposed system by implementing it in a statistical model and translating different influences from risk and protective factors to specific targets on the node and edge parameters of the symptom network. To analyze the behavior of the system under different targets, we present two novel network resilience metrics: Expected Symptom Activity (ESA, which indicates how many symptoms are active or inactive) and Symptom Activity Stability (SAS, which indicates how stable the symptom activity patterns are). These metrics follow standard practices in the resilience literature, combined with ideas from ecology and physics, and characterize resilience in terms of the stability of the system's healthy state. By discussing the advantages and limitations of our proposed system and metrics, we provide concrete suggestions for the further development of a comprehensive modeling approach to study the complex relationship between risk and protective factors and resilience.

3.1 INTRODUCTION

Understanding the causal background of psychiatric problems has been a central theme for psychiatry from its beginning as a medical discipline (Alexander & Elesnick, 1966; Harrington, 2019; Kraepelin & Lange, 1927; Shorter, 1997). For the vast majority of mental disorders, no conclusive single root causes have been found (Kendler, 2005, 2008), suggesting that psychiatric conditions may result from the interaction between many distinct factors (Kendler et al., 2011). As alternatives to monocausal biological and psychogenic approaches, holistic (e.g., biopsychosocial) theories have emphasized the ontological complexity of psychiatric disorders: in this view, a psychiatric disease has been conceptualized as the outcome of a dynamic interaction between biological, psychological and social variables (Engel, 1977; Ghaemi, 2008; Lamb, 2014; Wallace, 2008).

Despite their attractiveness, however, holistic ideas and concepts have often been stated in general and vague terms. Critics of holistic-dynamic approaches have, therefore, stressed the gap between recognizing the complexity of psychiatric disorders on the one hand and scientific rigor on the other (e.g., McLaren, 1998). However, there is no principled reason why holistic approaches could not be thoroughly scientific. To move towards more formalized holistic models of mental health, it has become increasingly popular to look at mental health systems using the lens of ecology (Olson & Goddard, 2010; VanLeeuwen et al., 1999). Ecosystem research studies the interactions between organisms and their environment, and is holistic in the sense that it conceptualizes these interactions as constitutive of a single integrated system (Chapin III et al., 2002; Folke et al., 2004; Scheffer et al., 2001). For example, according to the ecosystem approach to human development, humans are embedded within different ecological levels (Bronfenbrenner, 1979; Ungar, 2011). Interactions between individuals take place within a specific environmental context and are embedded within a broader cultural and sociological level.

A variety of risk and protective factors (henceforth: RP factors) exist in each of these ecological levels. Risk factors hinder optimal coping mechanisms, increasing the probability of negative outcomes when individuals are faced with adversity, while protective factors help individuals navigate adverse life events with less damage (Werner, 2000). RP factors are therefore closely related to the development of resilience, which is defined as the ability to maintain or quickly bounce back to a healthy state despite facing adversity (Kalisch et al., 2017; Rutter, 2012). Researchers have successfully identified a host of RP factors related to resilience across various domains such as (neuro)biology, personality, socio-economic factors, and family structures (e.g., Benzies & Mychasiuk, 2009; Friedman et al., 2016; Martinez-Torteya et al., 2009). For example, a frequently replicated risk factor for the development of posttraumatic stress disorder (PTSD) is childhood trauma (Isvoranu et al., 2016; Yehuda

et al., 2001). On the other hand, social support is an established protective factor against the development of depression in high-risk environments (Casale et al., 2015). Various brain structures and pathways have been found to be related to resilience (Liu et al., 2018). Furthermore, severe depression has consistently been associated with dysfunctions in biological stress responses, such as irregularities in the feedback-loop of the hypothalamic–pituitary–adrenal axis (HPA axis; Glass et al., 2004; Malhi & Mann, 2018).

However, in typical schematic representations of RP factors affecting mental health and resilience, it is easy to draw causal arrows between domains, such as neurobiological variables affecting psychological variables that, in turn, affect social variables. It is, however, more difficult to specify the exact nature of those causal arrows or to analyze how the system as a whole behaves as a function of these relations. Due to the multifactorial and complex nature of mental health, few would argue that the ecosystem analogy has to be correct in some way. However, current approaches are a) insufficiently precise, as suggestive visual representations of complex systems have not yet been translated into formal models, b) not operationalized, as there exist no widely accessible tools for modeling psychological resilience, and c) silent on crucial conceptual issues, such as how psychological, biological, and social factors interact or how different time scales are related.

In the current chapter, we address these issues by extending the network theory of psychopathology (Borsboom, 2017; Borsboom & Cramer, 2013) with RP factors and propose an approach to analyze the resilience of the resulting system. A recent theory by Kalisch et al. (2019) proposes that resilience factors target parameters of psychopathology networks. By doing so, these resilience factors influence symptom development patterns and improve resilience. We expand this idea to include both risk and protective factors and take a step forward in formalizing the system by representing it with a statistical model. We translate various effects RP factors can have on resilience to specific targets on network parameters. To analyze the resilience of this system, we introduce two novel resilience metrics for symptom networks: Expected Symptom Activity (ESA) and Symptom Activity Stability (SAS). These metrics are developed by combining standard practices in the resilience literature with ideas from the field of ecology and physics, where resilience is defined as a healthy state that is robust in stability. In Section 3.2, we outline the theoretical framework of the proposed system, after which we will present three studies that serve as illustrations of our system and resilience metrics (see Sections 3.3-3.5). Lastly, we will discuss the limitations of our proposed system and metrics and provide concrete suggestions for future research (see Section 3.6: General Discussion).

3.2 THEORETICAL FRAMEWORK: RP FACTORS TARGET THE ARCHITECTURE OF SYMPTOM NETWORKS

The main idea behind the network approach to psychopathology is that mental disorders act as a complex system, where psychopathology emerges from causally interacting symptoms connected in a network (Cramer & Borsboom, 2015). Symptoms are typically conceptualized as being present (possibly with some degree of severity) or absent, and accordingly modelled using an Ising model (van Borkulo, Borsboom, et al., 2014) or an extension thereof.

In these models, it is useful to specify two types of parameters. First, an activation parameter for every node (i.e., the network variables, in this case, symptoms), called the threshold parameter, which indicates the node's internal preference to be activated (van Borkulo, Borsboom, et al., 2014) or, alternatively, how much pressure is required to activate the node. For example, a node such as 'suicidal ideation' will have a stronger negative threshold, meaning it is more likely to be deactivated and will require more pressure to activate, than a node such as 'insomnia' which is more easily activated (Borsboom & Cramer, 2013). Second, a connectivity parameter for every estimated edge (i.e., the connection between variables), which indicates the weight, type, and directionality of every edge between two nodes. Edges can be strong or weak, positive or negative, and unidirectional or bidirectional (Epskamp & Fried, 2018). The set of node and edge parameters of the network model forms the network architecture, which describes, for example, if there are few or many edges between symptoms and if symptoms are more or less likely to activate.

Psychological networks are dynamic models, where network architecture governs symptom activation patterns (Borsboom, 2017). Activation of one symptom can lead to activation of a strongly connected neighboring symptom. If two symptoms, e.g., "fatigue" and "depressed mood", are connected, the theory states that activation of "fatigue" increases the probability of activating "depressed mood". The stronger the association between two symptoms (denoted in the connectivity parameter), the higher the probability that activation of one symptom leads to activation of the other symptom (Cramer et al., 2016).

If external stressors (e.g., losing one's job), are sufficient to trigger symptom activation and symptoms are strongly connected, the activation of one symptom could lead to a full activation spread where the network falls into a pattern of persisting symptom activation (Cramer et al., 2016). In contrast, if symptoms are not easily activated and/or weakly connected, an external stressor might lead to the activation of one or two symptoms but will not result in a full-blown depressive episode. In this way, network architecture determines the most likely symptom activation pattern (Borsboom, 2017).

Following this line of reasoning, if (1) psychopathology develops according to the network theory of mental disorders, and (2) network architecture is of paramount importance for symptom development, the next question is how this network architecture arises. Which factors contribute to the development of a 'healthy' or 'unhealthy' network architecture, increasing or decreasing the probability that a stressful event will trigger a whole symptom activation spread?

Until now, the network theory of mental disorders has mostly focused on psychopathology and symptom networks (Robinaugh et al., 2020). However, network theory also allows one to formalize biopsychosocial ecosystem models of mental health and resilience. Recently, an answer to how network architecture might arise has been proposed by extending symptom networks with resilience factors, which are called hybrid symptom-and-resilience-factor (HSR) networks (Kalisch et al., 2019). These resilience factors are represented as external, protective variables influencing symptom network architecture. In this way, resilience factors affect symptom development patterns and account for individual differences in resilience (Kalisch et al., 2019).

HSR networks need not be restricted to positive resilience factors. RP factors could both be present in these HSR networks (see Figure 3.1 for a representation of the theoretical model, including RP factors). For example, a protective factor such as "positive affect" could lower the strength of the connection between the symptoms "depressed mood" and "excessive worrying", making it less likely that the activation of depressed mood will lead to the activation of excessive worrying. Contrary, vicious cognitive thought patterns ("I am worthless", "I will never be good enough") might affect threshold parameters of specific symptoms, making it more likely that, for example, the Generalized Anxiety Disorder (GAD) symptom "excessive worrying" will be activated. Biological factors might also influence liability for developing psychiatric disorders, and possible biological pathways have been investigated by adding genetic risk scores to psychiatric symptom networks of psychosis (Isvoranu et al., 2019). Also, weak but differential relations have been found by adding biomarkers (estriol, cortisol, corticotropin-releasing hormone, and tumor necrosis factor alpha) to a symptom network of post-natal depression, suggesting possible symptom-specific biological pathways (Santos et al., 2017). Lastly, another example comes from the social domain, where social support has frequently been found to be a protective factor for developing Major Depressive Disorder (MDD; Gariépy et al., 2016). The social domain variable "social support" might function as a moderator between "Depressed Mood" and "Worthlessness". In other words, social support could lower connectivity strength between two MDD symptoms, thereby dampening the effect activation of depressed mood has on the development of feelings of worthlessness.

The theory that RP factors affect the architecture of the symptom network and, thereby, resilience (Kalisch et al., 2019) is a promising approach to formally study the

relationship between mental health and environmental RP factors from a complex systems perspective. However, the theory has not yet been formalized or translated to a statistical model, nor has it been used to analyze empirical data. We present three studies; the first two are simulation studies, which differ in that Study I analyzes the resilience of networks as a function of global effects from hypothetical RP factors (i.e., the whole network architecture is systematically altered), and Study II analyzes the resilience of networks under specific targets of hypothetical RP factors (i.e., parameters belonging to nodes with different roles in the maintenance and development of symptom activation are altered). Study III is an empirical study, in which we give an empirical illustration of the full system.

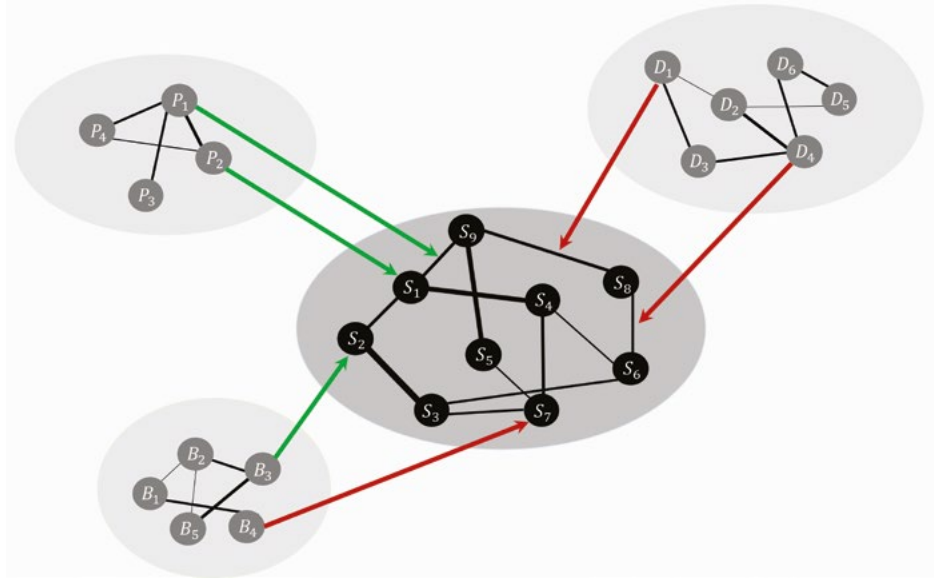

Figure 3.1. The theoretical ecosystem model of mental health. The psychopathology symptom network model, denoted with symptoms, S_1 to S_9, lays in the center (in black for illustrative purposes). Around the symptom network model forms a web of networks with variables from other domains, such as personality (P), biological (B), and social variables (D). Specific variables from other domains function as risk (red arrows) or protective (green arrows) factors, targeting node parameters or edge parameters. These risk and protective factors affect the symptom network model's architecture, thereby shaping the most likely symptom development pattern.

3.3 STUDY I: ANALYZING GLOBAL EFFECTS FROM RP FACTORS ON THE SYMPTOM NETWORK

In this study, we investigate how the resilience of a symptom network changes under global effects of RP factors – that is, RP factors have an effect on the whole network architecture. The model in this study is illustrated in Figure 3.2. Hypothetical RP factors (i.e., the peripheral networks containing variables Y1-Y4, Z1-Z4, and

V1-V4) affect the thresholds as well as the edges of a hypothetical, fully connected psychopathology network of symptoms (i.e., the center network containing variables X1-X9 with a density of 1). Risk factors deteriorate resilience (red arrows), protective factors increase resilience (green arrows). We systematically alter the strength of the effect of RP factors and the density of the symptom network. To analyze the resilience of the symptom network model, we present two novel resilience metrics: ESA, which indicates how many symptoms are active or inactive, and SAS, which indicates how stable the symptom activity patterns are.

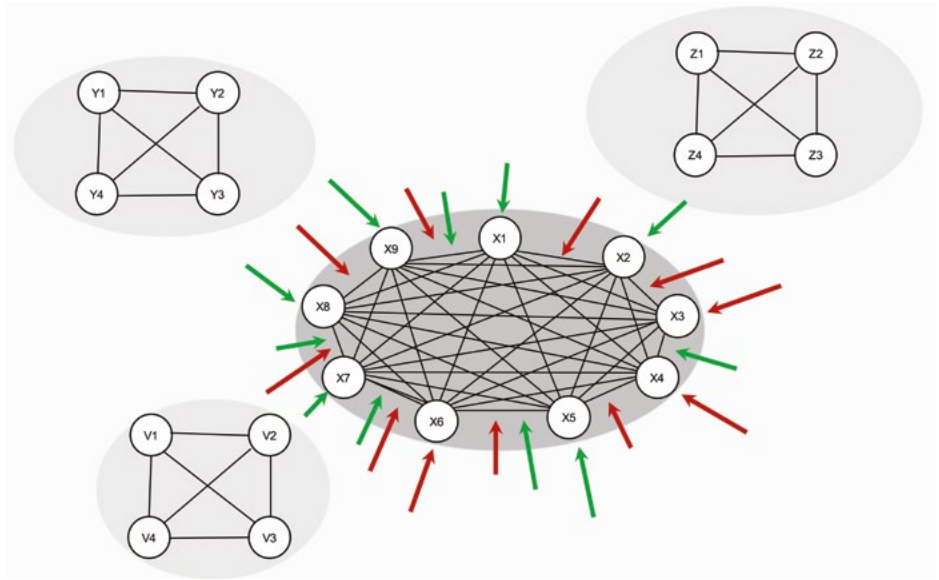

Figure 3.2. Design of Study I. The network in the centre represents the symptom network (containing variables X1-X9). The three remaining networks (containing variables Y1-Y4, Z1-Z4, and V1-V4) represent hypothetical RP factors. Since no empirical data is used, all variables are denoted in statistical interpretation, without substantive labels. RP factors are assumed to cause changes in symptom network architecture, but no data on RP factors are used in the study. All RP factors are assumed to affect the symptom network architecture equally.

3.3.1 Simulation study

3.3.1.1 The symptom network model

The symptom network model is represented by the Ising model (Ising, 1925). This model originates in the field of thermodynamics and ferromagnetism but has frequently been applied to represent psychological and psychiatric dynamical systems (see, for example: Cramer et al., 2016; Dalege et al., 2018; Marsman et al., 2017; van Borkulo et al., 2014) due to its relative simplicity in number and type of parameters and, nonetheless, its capacity to accommodate complex phenomena. For example,

in some parameter settings, the Ising model can show alternative stable states that the system converges towards, while in others, it can show linear, gradual changes (Cramer et al., 2016). Other characteristics of the Ising model are that relationships are undirected (e.g., the undirected arrow between X1 and X2 implies that the relationship from X1 to X2 is equal to the relationship from X2 to X1; see Figure 3.2) and that all nodes of the Ising model are binary (i.e., symptoms can be inactive; denoted by a 0, or active; denoted by a 1).

A substantial advantage of the Ising model is that it is analytically solvable up to around ten nodes (Epskamp, 2020), meaning the full probability distribution over all states is known and all model dynamics can be calculated from the model parameters. This allows for a complete overview of the model's behavior as a function of its architecture. For our study, this means that we know precisely how many active symptoms to expect for every parameter combination of the network, allowing us to study how the symptom network model behaves under different influences from hypothetical RP factors. We chose a network model with nine symptoms, mimicking the MDD symptoms proposed by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013). All threshold parameters have a value of -2, and all connectivity parameters have a value of 0.5.

3.3.1.2 Effects of RP factors on the symptom network

In the proposed system, RP factors affect the resilience symptom networks by targeting edges (connectivity parameters) or nodes (threshold parameters). In our simulation, targets are operationalized by multiplying specific parameters of the symptom network with certain constants. RP factors that affect edges act as causal *moderators* (Kalisch et al., 2019). Such risk moderators increase connectivity parameters (i.e., multiply the edge weights with a constant > 1), making it more likely that a symptom will activate its neighboring symptom. In contrast, protective moderators decrease connectivity parameters (i.e., multiply the edge weights with a constant < 1).

RP factors that affect nodes act as causal *main effects,* affecting threshold parameters. Risk main effects increase a symptom's disposition for activation. Since symptom threshold parameters are generally negative, risk factors make the thresholds less negative (i.e., multiply thresholds with a constant < 1). Contrary, protective main effects decrease a symptom's internal disposition for activation by increasing the negative value of threshold parameters (i.e., multiply thresholds with a constant > 1).

For symmetry, the constants < 1 range from 0.5 to 1 with a stepwise increase of 0.1, and constants > 1 are given by the inverse of the resulting numbers. Consequently, baseline network parameters are multiplied by 11 constants: 0.50, 0.60, 0.70, 0.80, 0.90, 1, 1.11, 1.25, 1.43, 1.67 and 2. A constant of 1 represents the baseline network without influences from risk or protective factors.

3.3.1.3 Network density

Symptom activity patterns will not only depend on the strength and type of targets from RP factors on the symptom network, but also, on the density *structure* of the symptom network (i.e., the proportion of present edges relative to all possible edges; van Borkulo et al., *in press*). Density influences network dynamics; the denser the network, the stronger symptoms interact and symptom activation is spread over the network (Bringmann et al., 2016). Therefore, we use networks with three different densities (1, 0.5, and 0.3) in our simulations (see Figure 3.3).

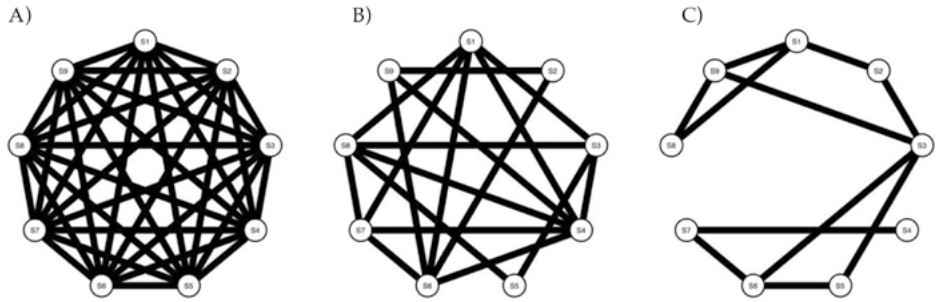

Figure 3.3. Three Ising models with varying densities. Panel (A; left) shows an Ising model with density = 1, panel (B; centre) shows an Ising model with density = 0.5 and panel (C; right) shows an Ising model with density = 0.3.

3.3.1.4 Metrics to assess resilience

To assess the resilience of our hypothetical symptom network, we introduce two novel resilience metrics. The ESA represents the mean sum score of active symptoms as a function of the network's underlying probability distribution. This informs us whether a network is likely to be in a healthy state (i.e., a low ESA due to weak symptom activity) or an unhealthy state (i.e., a high ESA due to strong symptom activity). Symptom levels are often used to assess the validity of resilience questionnaires by relating resilience scores to the severity of mental disorders (Connor & Davidson, 2003; Oshio et al., 2003). The rationale behind this is that individuals who score high on protective factors and/or score low on risk factors are more likely to develop fewer symptoms when faced with stressful life events than those who score low on protective factors and/or high on risk factors.

Resilience, however, is defined as the ability to maintain a healthy state (i.e., a low sum score) and quickly bounce back to a healthy state after facing adversity. In other words, a resilient system is characterized by a low ESA and *stable symptom activity.* To capture the latter characteristic, we introduce our second resilience metric, SAS, which involves the variability of the symptom activity pattern. Variability of symptom activity is an important aspect of resilience since the mean sum score can result from different activation patterns. For example, in a system with nine symptoms, a mean

score of 3 could be the result of consistently moderate or highly unstable symptom activity patterns. This means that a symptom network is resilient if ESA has a low value and SAS has a high value: in that case, the dominant state of the network is one in which symptoms are stably absent[3].

SAS is related to a model's *entropy*, which has been used as an indicator of stability in dynamic systems theory. Entropy is a measure of the probability of each possible state of the system, based on the parameters of the system (Dalege et al., 2018; Jaynes, 1965). If entropy is high, many states are equally likely, which indicates that the system's dynamics will be unstable, switching between many possible states. Contrarily, if entropy is low, only a few states have a high probability of occurring, meaning the system's behavior will be more organized and stable.

Symptom activation patterns follow from the probability distribution of the Ising model. The Ising model for two nodes (X_1, X_2) is given by formula (1), which extends for models with n nodes (Haslbeck et al., 2020):

$$P(X_1, X_2) = \frac{1}{Z}\exp\{\tau_1 X_1 + \tau_2 X_2 + W_{12} X_1 X_2\} \quad (1)$$

In this formula, X_1 and X_2 are elements of {0,1}, $P(X_1, X_2)$ is the probability of the event (X_1, X_2), τ_1 denotes the threshold parameter of the node X_1, and W_{12} denotes the edge weight parameter of the neighboring nodes X_1 and X_2. Z is a normalizing constant denoting the sum of the potentials of all possible states. The probability distribution for n = 9 can be calculated by a generalization of formula (1).

ESA is calculated by taking the expected value E(.) of the probability distribution:

$$E(Y) = \mu = \sum_{i=0}^{n} P(Y_i) Y_i \quad (2)$$

Where Y represents the number of active symptoms in the network (i.e., Y ranges over all possible sum scores; in our case from 0 to 9), Y_i represents a possible sum score i, and $P(Y_i)$ represents the corresponding probability of Y_i given a specific network architecture. This probability distribution is provided the *IsingSampler* package in the R-programming environment (Epskamp, 2020).

3 Note that SAS can be low when ESA is low or when ESA is high. Although the symptom network is stable in both cases, it is not resilient in its healthy state for the latter case. Also note in many cases there will be a strong relation between ESA and SAS, in the sense that SAS will be lowest if ESA hovers around $n/2$ and will increase as ESA approaches its limits at 0 or n. However, one can also set up parameter settings for the network in which ESA equals $n/2$ and SAS is high (this will occur, for instance, if half of the symptoms have a very strong threshold and the other have a very weak threshold); hence, even though ESA and SAS will often be related, this is not necessarily so.

SAS is calculated by taking the inverse of the standard deviation σ of the expected value $E(Y)$:

$$\sigma = \sqrt{\sum_{i=0}^{n} (Y_i - \mu)^2 P(Y_i)} \quad (3)$$

The standard deviation is a scaled variability metric. We take its inverse to align the magnitude of SAS with its interpretation: low SAS indicates weak stability, and high SAS indicates robust stability. Taking a standard deviation of 1 as a reference, SAS – the inverse of the standard deviation – is also 1. When the standard deviation is larger than 1, SAS will be < 1, indicating that the stability is lower. When the standard deviation is smaller than 1, SAS will be >1, indicating that the stability is higher. We calculate $P(Y_i)$ for every change of the network architecture using *IsingSampler* (Epskamp, 2020).

ESA and SAS will be calculated for all 11 network architectures, for all three networks with different densities.

3.3.2 Results

Results for all alterations (i.e., strength of effect of RP factors and density) on the architectures of the networks are displayed in Figure 3.4. Table 3.1 shows the results for the extremes of RP factor influences, namely when the multiplier is equal to 0.5 or 2.

For the model with density = 1, RP main effects and moderators strongly affect the resilience of the symptom network. In the absence of RP effects (i.e., multiplier = 1) ESA is moderate, and SAS is low, meaning that symptom activity is moderate but unstable. Protective factors decrease ESA and increase SAS, meaning that they push the network towards a resilient state. Contrary, risk factors strongly increase ESA and SAS, meaning that they push the network towards a stable state of high symptom activation. This means that as RP factors affect network parameters, symptom activity increases or decreases, and symptom development patterns become more stable. When RP factors simultaneously alter both connectivity and threshold parameters, ESA remains around its baseline value, with low ESA, indicating unstable activity patterns.

Dynamics change for the model with a density of 0.5. In the absence of RP factor effects (i.e., multiplier = 1) ESA is low, and SAS is moderate, meaning symptom activity patterns are low and relatively stable. However, risk moderators affecting edges increase ESA to moderate symptom activity and decrease SAS, meaning that risk moderators push the system towards an unhealthy and unstable state. Since there are fewer present edges that can be targeted by moderators, their effect on ESA is smaller compared to the fully connected network. This means that the network gets

pushed into moderate symptom activity with corresponding instability. Main effects targeting thresholds have a more substantial effect on resilience, as they still target all threshold parameters. Protective main effects push the system in the same resilient state as the former model with density =1.

The model with density = 0.3 follows similar dynamics as the former model with density = 0.5; however, ESA changes within a more restricted range, meaning effects from risk and protective factors on ESA are smaller.

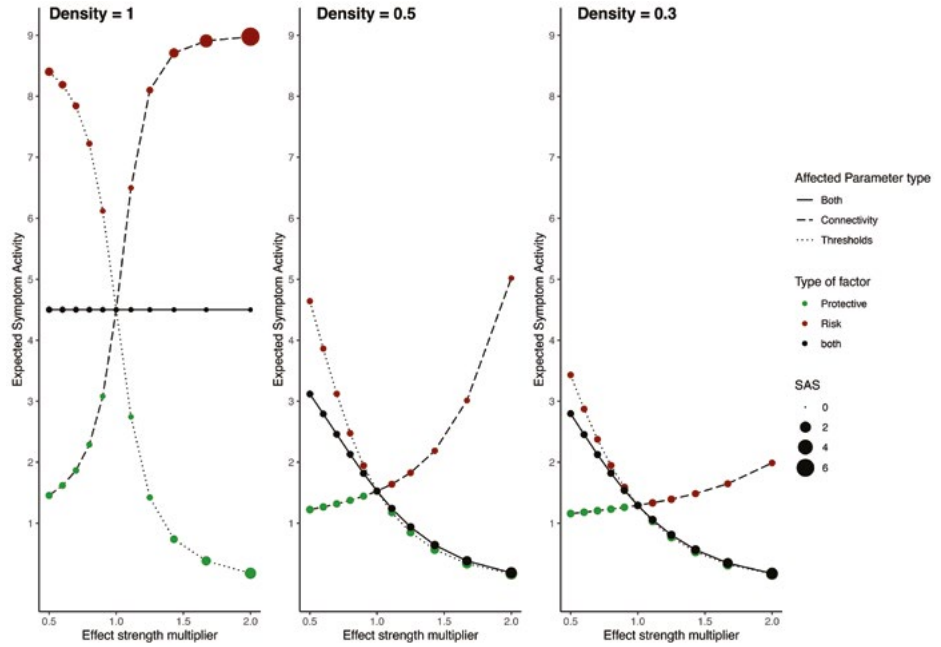

Figure 3.4. Risk and protective factors affecting symptom network dynamics. The behavior of an Ising model under the influences of hypothetical RP factors for three different network densities. The left panel shows a network with density = 1, the middle panel a network with density = 0.5, and the right panel a network with density = 0.3. The x-axis denotes the value of the constant with which network architecture is multiplied. The y-axis denotes ESA. Line type represents which parameters are multiplied; threshold parameters, connectivity parameters, or both. The color of circles represents the type of hypothetical RP factor which influences network parameters: red circles represent risk factors, green circles, protective factors, and black circles represent both factors. The size of the circles represents SAS.

Table 3.1. Network resilience for different densities and influences from risk and protective factors.

Factor Type	Density = 1		Density = 0.5		Density = 0.3		Multiplier
	ESA	*SAS*	*ESA*	*SAS*	*ESA*	*SAS*	
Baseline	4.5	0.34	1.53	0.74	1.29	0.86	1
Moderator							
Risk	8.98	6.47	5.02	0.39	1.99	0.60	2
Protective	1.46	0.77	1.22	0.91	1.15	0.96	0.5
Main Effect							
Risk	8.40	1.08	4.64	0.51	3.43	0.59	0.5
Protective	0.18	2.26	0.17	2.39	0.17	2.44	2
Both	4.5	0.49	3.12	0.62	2.80	0.67	0.5
	4.5	0.23	0.19	2.16	0.18	2.32	2

ESA stands for Expected Symptom Activity, which describes the level of symptom activity. ESA ranges between 0 and the total number of symptoms, in this case, 9. Low ESA means a low level of activity, indicating a healthy state. SAS stands for Symptom Activity Stability, which describes the stability of symptom activation patterns. SAS is computed as the inverse standard deviation, meaning an SAS of 1 indicates a standard deviation of 1. SAS < 1 indicates decreasing stability (increasing standard deviation), and SAS > 1 indicates increasing stability (decreasing standard deviation). A system is resilient when ESA is low and SAS is high, as this indicates a low level of symptom activation with robust stability.

3.3.3 Discussion

In Study I, we investigated the resilience of symptom networks with varying densities and different degrees of the effect of RP moderators and main effects by inspecting ESA and SAS. Results from this simulation study show that the resilience of the network changes as a result of RP effects. However, network density also strongly affects how resilience changes. When density is 1 (i.e., a fully connected network) and risk factors target the network, ESA increases, and SAS decreases. This means that the model is in a disorder state with full symptom activity and is unlikely to recover from this. Contrary, when protective factors target the network, ESA decreases, and SAS increases. This means that the network shows strong resilience, as symptom activity is low, but stability is high.

However, as density decreases, the network's ESA also decreases, meaning that it never shows full activity in our simulations. Risk factors, especially moderators (i.e., affecting edge parameters), increase ESA and decrease SAS, implying that stability decreases as risk factors gain more influence. When both RP factors are present, the main factors affecting thresholds have a more substantial influence on ESA than moderators affecting connectivity parameters. This is due to the fact that there are

fewer present edges moderators can influence, and therefore, their effect on symptom activation patterns is smaller.

3.4 STUDY II: MANIPULATING THE TARGET POINTS OF THE RP FACTORS ON THE SYMPTOM NETWORK

A fundamental principle of network theory is that nodes differ in how important they are in maintaining and developing symptom activity (Blanken et al., 2018; Borsboom, 2017). In this study, we investigate how the resilience of a symptom network changes when target points of RP factors affect parameters belonging to nodes that have a strong or weak role in symptom activity spread. The model in this study is illustrated in Figure 3.5. Hypothetical RP factors (i.e., the networks containing variables Y1-Y4, Z1-Z4, and V1-V4) affect specific threshold and edge parameters of the psychopathology symptom network (i.e., the center network containing variables S_1 - S_9. The symptom model is estimated from empirical data to obtain plausible network parameters that differ per node and edge (i.e., the symptoms vary in their importance on symptom activity spread). We systematically alter parameters belonging to nodes with a weak or strong role in the symptom network.

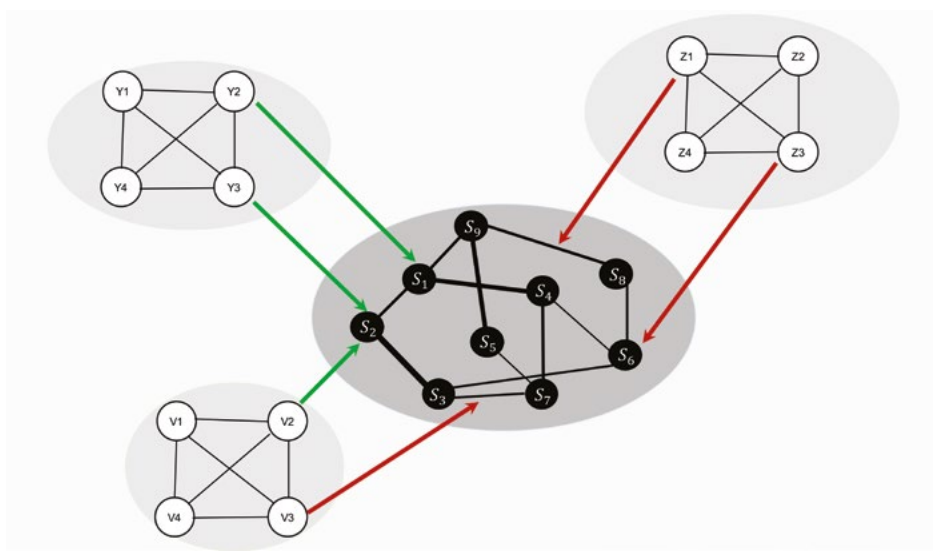

Figure 3.5. The design of Study II. The network in the centre represents the symptom network (variables S_1 to S_9). The symptom network is estimated from empirical data. Therefore, edge and node parameters differ, leading to different roles symptoms have in the spread of symptom activity. The three remaining networks (containing variables Y1-Y4, Z1-Z4, and V1-V4) represent hypothetical RP factors. RP factors are assumed to change symptom network architecture, by systematically targeting symptom network parameters. We study how different target points from RP factors on symptom network architecture affect resilience, by multiplying specific symptom network parameters with constants.

3.4.1 Simulation Study

3.4.1.1 Data

Psychiatric symptoms are measured with the 27-item Symptom Checklist (SCL-27; Hardt & Gerbershagen, 2001). The SCL-27 is a multidimensional screening instrument, functioning as a validated abbreviation of the 90-Symptom Checklist (Derogatis et al., 1973). It consists of 27 items measuring symptoms on six dimensions: (I) depressive symptoms, (II) dysthymic symptoms, (III) vegetative symptoms, (IV) agoraphobic symptoms, (V) symptoms of social phobia, and (VI) symptoms of mistrust. Symptom descriptions can be found in the supplementary materials. Symptoms are measured on an ordinal scale with five levels. Participants were part of an Argentinian study on mental health and were recruited via probability sampling (Etchevers et al., 2019). Number of participants is 1469 (female = 875, male = 579, other = 15). The questionnaire was administered online.

3.4.1.2 The symptom network model

An Ising model is used to estimate the network model (see Figure 3.6). In order to estimate the Ising model, the data need to be binarized. The following rule is used: responses indicating no or modest symptom presence are recoded with a 0, responses indicating moderate or high symptom presence are recoded with a 1. Thus: {0, 1, 2} → 0, {3, 4} → 1. The model is estimated using the *IsingFit* package in the R-programming environment (van Borkulo et al., 2014).

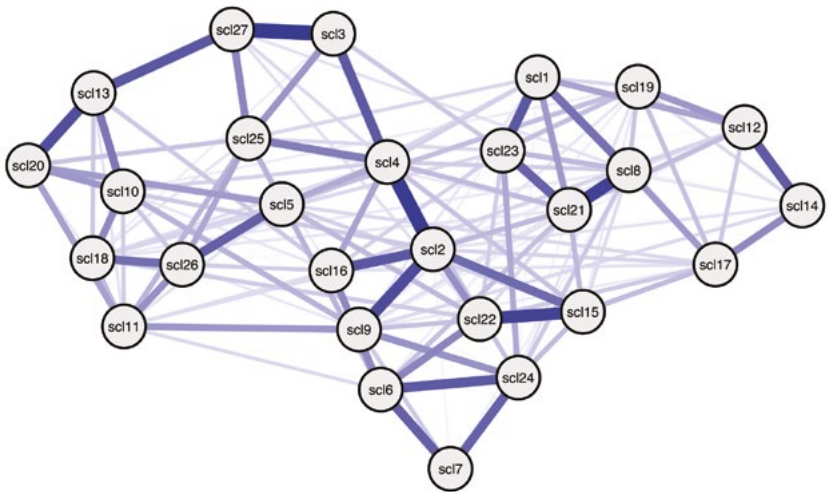

Figure 3.6. Empirically estimated symptom network. Empirically estimated Ising model using SCL-27 symptom data. Blue edges represent positive associations between nodes (van Borkulo et al., 2014a). The width of edges and color intensity represents the strength of edges, showing the connectivity parameters in this estimated model differ for every pair of nodes. Threshold parameters differ per node. Symptom descriptions can be found in the supplementary materials.

3.4.1.3 Calculate ESA and SAS from simulated Ising model dynamics

Since the estimated Ising model consists of 27 nodes, the underlying probability distribution cannot be calculated analytically. Instead, we need to simulate data points using a sampling method. The *IsingSampler* package in the R-programming environment includes three sampling methods to simulate states from an Ising model. We will use the Metropolis-Hastings algorithm (Murray, 2007). The chain starts with random values for every node, consisting of a 0 or a 1 (indicating presence/absence of the symptom). Then, for every iteration, a node is set to its opposite response option, and the probability of that node being in the opposite option given all other node values and parameters is calculated. In this way, the chain converges to the most probable state of the model based on its parameters. We use 1000 iterations for every chain.

ESA is calculated by taking the mean sum score and SAS by taking the inverse standard deviation of the 1000 simulated data points.

3.4.1.4 Strong nodes and weak nodes

Some nodes could be more involved than others in the spread of symptom activity when they are more central than others (Fried et al., 2016). Centrality indices describe how strong nodes are connected with other nodes and/or how many connections they have with neighboring nodes (Epskamp, Waldorp, et al., 2018). Nodes with many strong associations are hypothesized to have a more substantial influence on symptom development patterns. Different centrality indices exist, but, currently, *node strength* is the most stable one (Epskamp, Borsboom, et al., 2018). Therefore, we use node strength to determine which nodes are targeted by RP factors. Node strength centrality is calculated by taking the sum of all absolute edge weights a node is directly connected to (Bringmann et al., 2019).

Figure 3.7 shows the node strength indicator for every node, ordered from high node strength to low node strength. The five nodes with the highest node strength are SCL-2, SCL-4, SCL-8, SCL-9, and SCL-21, which will be called *strong nodes*. The *weak nodes* are the five nodes with the lowest node strength: SCL-3, SCL-7, SCL-14, SCL-19, and SCL-20.

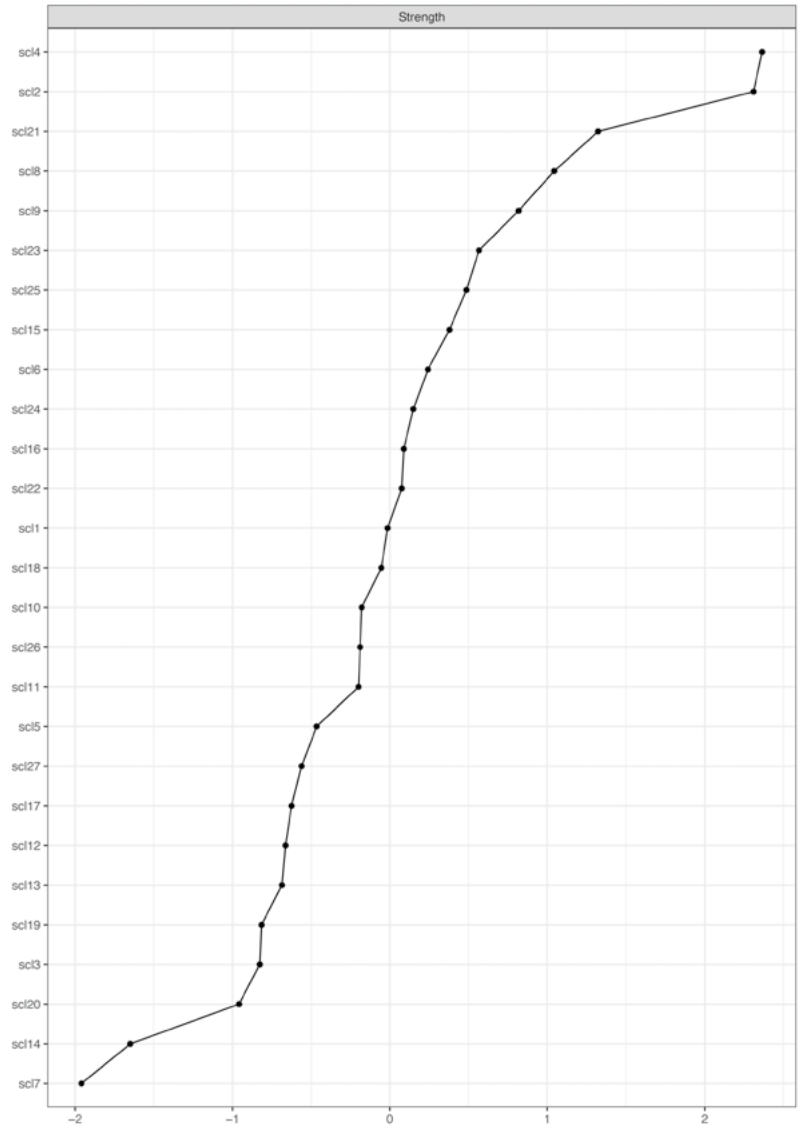

Figure 3.7. Centrality plot showing the node strength of SCL-27 symptoms. The x-axis shows node strength on standardized z-scores; the y-axis shows all SCL-27 variables. The variables are ranked from highest to lowest node strength.

We create two conditions, the strong node condition, and weak node condition. In both conditions, threshold and connectivity parameters are systematically altered using the same 11 multiplying constants from Study I. In the strong nodes condition, parameters belonging to strong nodes are altered, and in the weak nodes condition, parameters belonging to weak nodes are altered (see Figure 3.8; yellow edges and nodes represent connectivity parameters and threshold parameters that are altered

for every condition). For every alteration, symptom activation is simulated using the *IsingSampler* package (Epskamp, 2020) and ESA and SAS are calculated from these simulated symptom dynamics.

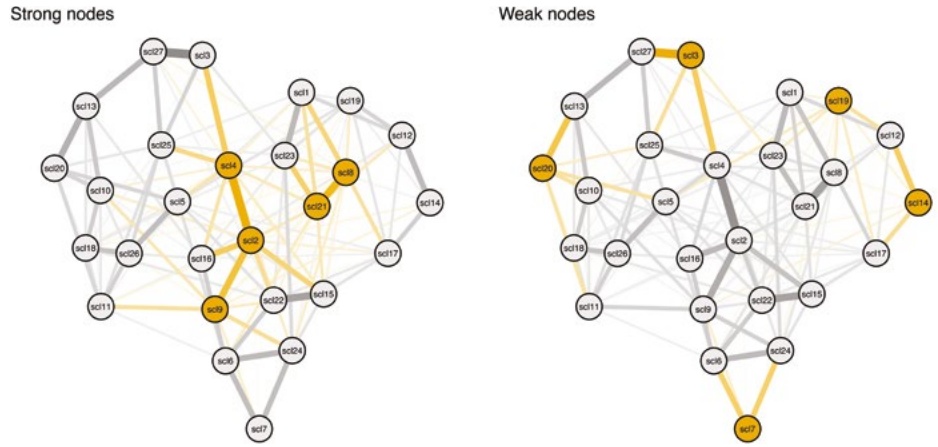

Figure 3.8. Targeting parameters of strong and weak nodes. Yellow nodes and edges represent targets in the simulation. Targets are based on nodes with highest (left panel) and lowest (right panel) node strength. Symptom descriptions can be found in the supplementary materials.

3.4.2 Results

Here we will discuss the general results from the simulation study. Figure 3.9 shows the complete results, including all alterations on the network architectures, and Table 3.2 shows the results for the extreme values influences from RP factors, i.e., when the constant used as multiplier is equal to 0.5 or 2.

Baseline ESA (i.e., when the constant used as multiplier = 1) for the model is low, meaning that the sample is healthy. However, baseline SAS is also low, meaning that this healthy state is unstable. In the strong nodes condition, risk factors strongly increase ESA and maintain SAS, meaning that they push the network towards a state of higher symptom activity, however, maintaining its instability. Protective factors decrease ESA and increase SAS, meaning they push the system towards a resilient state. When RP factors target connectivity and threshold parameters simultaneously, dynamics fluctuate within a wider range of ESA and SAS, nonetheless, maintaining a relative healthy and stable state.

In the weak nodes condition, RP factors have a smaller effect on resilience. Risk factors increase ESA; however, they have a weaker effect compared to the strong nodes condition. SAS is further decreased, meaning that the system is pushed towards an unstable state of moderate symptom activity. Protective factors decrease ESA but have a more moderate effect on lowering ESA compared to the strong nodes condition.

When both RP factors target connectivity parameters and threshold parameters simultaneously, they maintain SAS at its baseline level, while ESA fluctuates within a smaller range compared to the strong nodes condition.

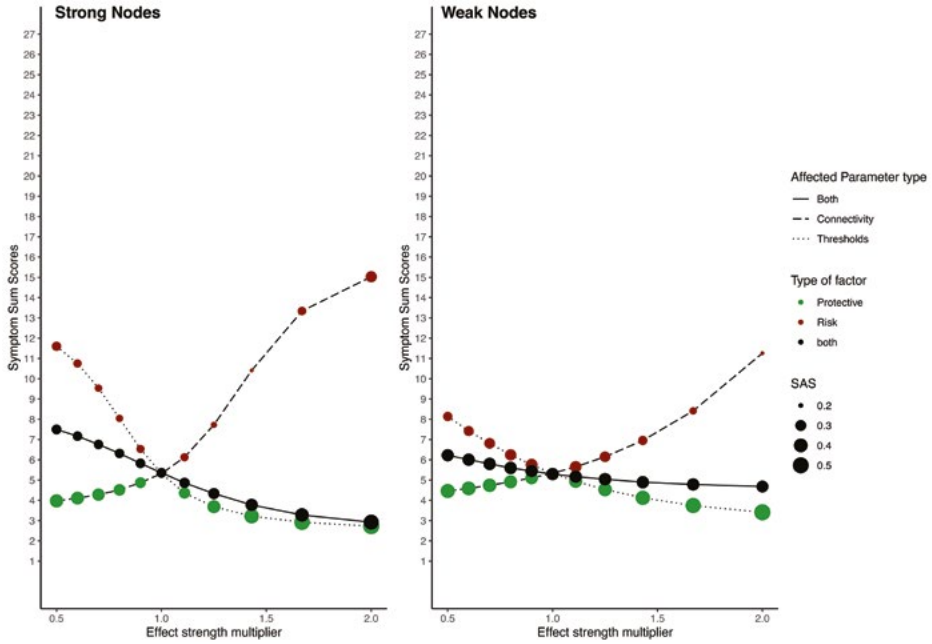

Figure 3.9. Risk and protective factors affecting parameters of strong and weak nodes. The behavior of an estimated Ising model under influences of hypothetical RP factors, when parameters belonging to nodes with high and weak node strength are targeted. The left panel shows the network behavior in the strong node condition; the right panel shows its behavior in the weak node condition. The x-axis denotes the value of the multiplier constant. The y-axis denotes ESA. Line type represents which parameters are multiplied; threshold parameters, connectivity parameters, or both. The color of circles represents the hypothetical RP factor that influences network parameters: red circles represent risk factors, green circles, protective factors, and black circles represent both factors. The size of the circles represents SAS.

Table 3.2. Risk and protective factors influencing strong or weak nodes.

Factor Type	Strong nodes		Weak nodes		Multiplier
	ESA	*SAS*	*ESA*	*SAS*	
Baseline	5.32	0.27	5.34	0.27	1
Moderator					
Risk	15.03	0.31	11.26	0.18	2
Protective	3.97	0.39	4.46	0.32	.5
Main Effect					
Risk	11.60	0.26	8.14	0.22	.5
Protective	2.72	0.53	3.41	0.38	2
Both	7.50	0.27	6.22	0.27	.5
	2.92	0.46	4.68	0.26	2

ESA stands for Expected Symptom Activity, which describes the symptom activity levels. ESA ranges between 0 and number of symptoms, in this case, 27. Low ESA indicates low activity levels, meaning the system is in a healthy state. SAS stands for Symptom Activity Stability, which describes the stability of symptom activity levels. SAS is computed by taking the inverse standard deviation. An SAS of 1 indicates a standard deviation of 1, SAS < 1 indicates decreasing stability (increasing standard deviation), and SAS > 1 indicates increasing stability (decreasing standard deviation). Low SAS indicates unstable symptom activity patterns. A system is resilient when ESA is low and SAS is high, meaning that the system has a stable and low level of symptom activity.

3.4.3 Discussion

We conclude that it matters which parameters are targeted by RP factors. RP factors altering parameters belonging to strong nodes have a more substantial effect on resilience than weak nodes. The range of ESA is wider in the strong nodes condition than in the weak nodes condition. Our study shows that risk factors in the strong nodes condition have a larger effect on ESA and SAS than risk parameters in the weak nodes group. However, this group difference does not hold for protective factors. This could be related to the health of the used sample, where baseline ESA is low.

Specific relations between RP factors and symptoms need to be estimated on the individual symptom level to understand how RP factors affect resilience. Therefore, in the next study, the effect of RP factors on resilience will be calculated by estimating a model from empirical data on RP factors and symptoms. This means that the associations between RP factors and specific symptoms will be empirically estimated. In this way, the effect of RP factors on specific symptoms can be studied.

3.5 STUDY III: EMPIRICAL ILLUSTRATION OF A SYSTEM INCLUDING SYMPTOMS AND RP FACTORS

In this section, we present an empirical illustration of how the proposed system can be implemented in a model that is estimated from data, including measurements on RP factors and psychiatric symptoms. We investigate which specific RP factors are associated with specific symptoms, and how symptom activity levels change when they are targeted by associated RP factors. Contrary to the former two simulation studies, no data will be generated, nor will network architecture be altered on hypothetical target points. Instead, we estimate a network that includes both symptoms and the RP factors which allows us to study possible symptom-specific pathways with RP factors and the system as a whole.

3.5.1 Study design

3.5.1.1 Data

We use the same dataset as the former study and include the measurements on RP factors from the same participants. RP factors are determined a priori; meaning factors are labelled as 'risk' or 'protective' before data are collected. Risk factors include measurements on tobacco use, alcohol use, and illicit drug use. Protective factors include measurements on physical activity, religious practice, sexual life satisfaction, and volunteer work.

Variables in this dataset are measured on different scales. The variables physical activity, tobacco use, alcohol use, and illicit drug use are measured on a binary scale, religious practice and volunteer work are measured on an ordinal scale (five levels), and sexual life satisfaction is measured on an ordinal scale (six levels). All variables are recoded such that '0' indicates no presence of the variable and '1' or higher indicates (increasing) presence. SCL-27 items representing symptoms (Derogatis et al., 1973) are measured on an ordinal scale (five levels).

Due to high correlations between the three risk factors, tobacco use, alcohol use, and illicit drug use, these factors have been collapsed into one risk factor, "substance use". This was done by summing over all three factors, which originally were measured on a binary scale, where 0 indicated no usage and 1 indicated usage. The novel "substance use" variable ranges from 0 to 3.

3.5.1.2 Model

In order to account for the different measurement scales used in the data, a Mixed Graphical Model (MGM; Haslbeck & Waldorp, 2020) is estimated. This network model includes both categorical and continuous variables. Here we choose to model ordinal variables as continuous variables.

The model uses nodewise regression to calculate associations between nodes (Haslbeck & Waldorp, 2020). For every variable, its intercept, and the beta-coefficients of all other variables are computed. This intercept represents the threshold of the node, and the beta-coefficients represent connectivity parameters with neighboring nodes. Regularization is applied to select the sparsest model, meaning that most edges with small values are pushed towards zero to control for false-positive edges (Epskamp & Fried, 2018).

The MGM estimates which variables are positively or negatively associated with each other. These associations represent main effects: if, for example, the variables "alcohol use" and "SCL-2: feeling blue" are positively connected, this means that if "alcohol use" increases, "SCL-2: feeling blue" increases as well. Keep in mind that this relationship could also be the other way around, which we will discuss further in Section 3.6 (General Discussion). The MGM is estimated using the *bootnet* package in R with the *mgm* default, using 10-fold cross-validation to select the regularization parameter (Epskamp, Borsboom, et al., 2018).

Moderation analysis is used to study which RP factors could influence connectivity parameters of the symptom network. This analysis checks for every relationship between RP factors and symptoms if another variable moderates this relationship. This is done by estimating a *Moderated Network Model* (MNM; Haslbeck et al., 2019) using the *mgm* package in R (Haslbeck & Waldorp, 2020).

3.5.1.3 Assessing resilience

In this study, we investigate how symptom activity levels change due to the presence or absence of RP factors. To study how RP factors affect symptom activity levels and stability, we condition on different values of these RP factors. Lowest values of RP factors indicate absence, highest values indicate their presence. The means of symptoms and possibly also the interactions between symptoms can be functions of the RP factors. If we condition on the RP factors we fix them to specific values, which affects the means and possibly interactions between symptoms. The effect of RP factors' presence or absence is calculated by conditioning on these RP factor values[4]. For example, conditioning on the presence of the protective factor "volunteer

4 Mathematically, in the regression formula used for calculating symptom means, the beta-coefficient (representing the connectivity parameter) of the corresponding RP factor is multiplied by a specific value of this RP factor instead of on the RP factor's mean. The effect of RP factors' presence or absence is calculated by conditioning on these RP factor values. However, when estimating the MGM, variables are standardized. This means model parameter estimates need to be transformed in order to be unbiased for computing ESA on the data scale (Hastie et al., 2015). Take β to be the unbiased beta-coefficients where: $\beta = (\beta_1, \beta_2, \ldots \beta_p)$ and $\hat{\beta}$ the biased beta-coefficients. The unbiased beta-coefficients can be calculated with: $\beta = \hat{\beta} * \frac{\sigma y}{\sigma x}$, where σy and σx are the original data standard deviations. The unbiased intercept can be calculated with:

$\hat{\beta}_0 = \bar{y} - \sum_{j=1}^{p} \bar{x}_j \hat{\beta}_j$, where $\bar{y}$ and $\{\bar{x}_j\}_1^p$ are the original data means.

work", is done by conditioning on its highest value, which is 5. The rest of the RP factors maintain their mean value. Based on the model, the novel symptom means are computed for the situation where "volunteer work" has a value of 5.

We investigate two situations by conditioning on the RP factors. In the first situation, we condition on the presence of protective factors, meaning item scores on protective factors are >= 1, and absence of risk factors, meaning item scores on risk factors are 0. Second, we study the opposite situation, namely, the presence of risk factors and the absence of protective factors. In both situations, novel symptom means for all SCL-27 items are computed. Note that it is not necessary that all symptoms will change in their means, since mean changes depend on whether a symptom mean is a function of the RP factors. In other words, if a symptom such as "SCL-6: your mind going blank" is not associated with any RP factors, and neither are its neighboring symptoms, the SCL-6 symptom mean will not change despite conditioning on any RP factor.

To compare symptom activity levels from the baseline model with the two conditioned situations representing the presence and absence of specific RP factors, ESA is computed in the baseline model and two conditioned models. Baseline symptom activity can be calculated from the data by calculating the individual symptom means of all the SCL-27 items. The novel, conditioned symptom means are computed after conditioning on the presence/absence of the RP factors. ESA is calculated by summing over all (conditioned) symptom means.

SAS will not be computed since, in the current analysis, ESA variance does not relate to symptom activity stability. Conditioning on RP factors does not change the variance patterns in symptoms. To compute SAS, the probability distribution of the whole model needs to be known, which is problematic in its current set-up because data are measured on a larger scale compared to the Ising model's binary case. A possible solution for future research is to gather longitudinal data, as will be further discussed in Section 3.6 (General Discussion).

To interpret current analyses outcomes using results from the former theoretical simulations, network density and node strength centrality of the symptom nodes will be computed. Density will only be computed for edges between symptom nodes.

3.5.2 Results

Figure 3.10 shows the estimated network model. The risk factor "substance use" is negatively associated with protective factors "religious practice" and "volunteer work". Surprisingly, there are also some negative edges between the risk factor and symptoms, such as the SCL-5 symptom "thoughts of death or dying".

Protective factors are mostly positively associated with each other and negatively associated with symptoms. For example, the protective factor "religious practice" is negatively associated with the SCL-15 symptom "Feeling hopeless about the future", the protective factor "sports / physical activity" is negatively associated with the SCL-9 symptom "Feeling low in energy or slowed down", and the protective factor "sexual life satisfaction" is negatively associated with the SCL-2 symptom "feeling blue".

No moderators between symptoms and RP factors have been found.

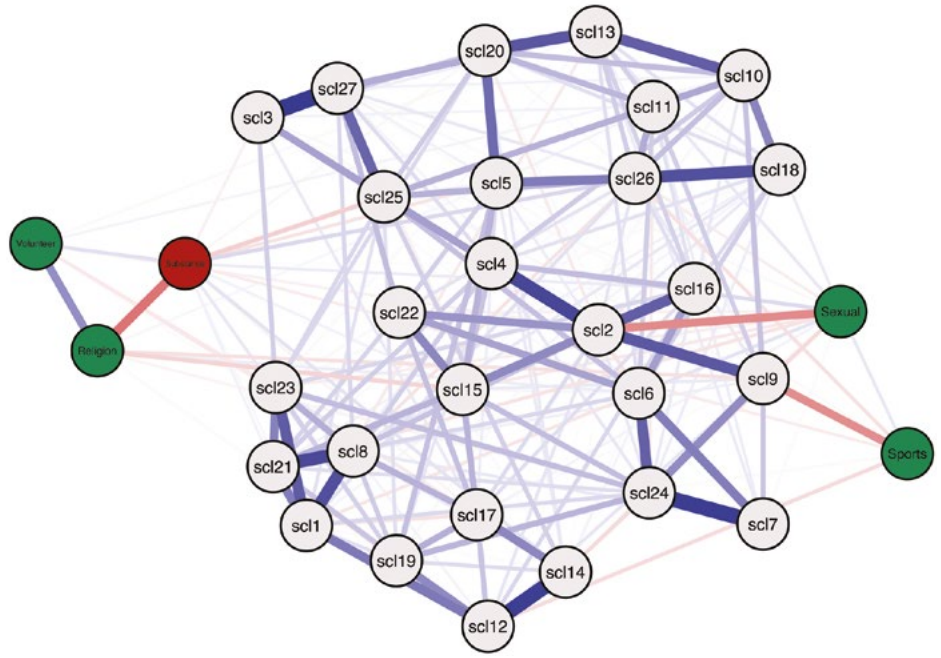

Figure 3.10. Mixed Graphical Model including symptoms and risk and protective factors. Grey nodes represent SCL-27 symptoms. Green nodes represent protective factors; red nodes represent risk factors. Blue edges represent positive associations, and red edges represent negative associations. The width of edges and color intensity represents edge strength. Node label abbreviations of the risk and protective factors are as follows: "Substance" refers to "Substance use", "Sports" to "Physical/sports activity", "Religion" to "Religious practice", "Sexual" to "Sexual life satisfaction", and "Volunteer" to "Volunteer work". The SLC-27 items can be found in the supplementary materials of this chapter (see Table D1).

The network density of edges between symptom nodes is 0.55. Nodes with the highest node strength are SCL-2, SCL-24, SCL-4, SCL-1, SCL-21 (see the supplementary materials for the centrality plot). All strongest symptoms are connected to at least two RP factors, although they have small edges.

The ESA of the baseline model is 36.21. Highest possible ESA is 4 * 27 = 108. When conditioning on the presence of protective factors and the absence of the risk factor, ESA decreases to 35.45. The difference with baseline ESA is – 0.75. When conditioning on the presence of the risk factor and the absence of protective factors, ESA is 36.70, meaning an increase of 0.49 compared with baseline ESA.

3.5.3 Discussion

We studied symptom-specific associations with RP factors, and the effect of the presence or absence of RP factors on symptom levels. Overall, protective factors were positively associated amongst each other and negatively associated with specific symptoms. The risk factor "substance use" was mostly positively associated with specific symptoms, however, there were also some negative associations with specific symptoms. No moderators were found.

When conditioning on the presence of the risk factor and the absence of protective factors, ESA slightly increased. Contrary, when conditioning on the presence of protective factors and the absence of the risk factor, ESA slightly decreased. This means that there is a small effect from the RP factors on symptom activity levels, where risk factors slightly decrease and protective factors slightly increase symptom activity. Note, however, that estimated edges are bidirectional. To investigate causal effects, longitudinal data are needed to estimate a dynamic model. Longitudinal data are furthermore needed to calculate SAS.

A possible explanation for the small effect of the RP factors on ESA is that floor effects might be present since baseline symptom activity levels are low. The sample contains too many healthy participants, meaning not enough participants are present showing high symptom activity and strong effects with risk factors. Including clinical patients in the sample might show a wider variety of response patterns and stronger effects when conditioning on RP factors.

Furthermore, the symptom network consisted of 27 items, while the RP factors consisted of merely five variables. Important RP factors which have a strong influence on the symptom network might be missing. Future studies could repeat the proposed analyses on a dataset with more RP factors to investigate if stronger effects are found.

The symptom network density is 0.5, meaning the range in which ESA could change is smaller, and the strongest nodes are connected to at least two, but not all, RP factors. Estimated edges have a much smaller value than the theoretical simulations' multipliers, explaining why this empirical illustration shows almost no effect.

3.6 GENERAL DISCUSSION

In this chapter, we presented a formal system where RP factors from biopsychosocial domains influence resilience by altering the architecture of psychopathology symptom networks. Furthermore, we presented two novel metrics to analyze the resilience of symptom networks. Here, we will discuss these contributions and their clinical implications, together with their limitations, and provide concrete suggestions for future research.

Our presented system builds on the theory by Kalisch et al. (2019), who propose that resilience factors could affect the architecture of symptom networks. By doing so, resilience factors change the network's symptom activity patterns and resilience. In this chapter, we extended that idea to include both risk and protective factors and took a step forward into formalizing the system. We translated possible ways in which RP factors can affect resilience to specific target points on the symptom network parameters, where we made a distinction between main effects targeting threshold parameters and moderators targeting connectivity parameters. Targets from RP factors are operationalized by multiplying these threshold and connectivity parameters with certain constants, which, based on their magnitude, act as risk or protective factors, thereby deteriorating or improving resilience. As a first formalization, we implemented the system using the Ising model as a statistical model representing the symptom network (van Borkulo, Borsboom, et al., 2014). Furthermore, we provided an empirical illustration of how the system could be implemented in a Mixed Graphical Model (Haslbeck & Waldorp, 2020), which analyzes both categorical and continuous data.

A second contribution of the current chapter is that we presented two novel metrics for assessing the resilience of symptom networks: Expected Symptom Activity (ESA) and Symptom Activity Stability (SAS). Computing ESA is based on the common practice in the resilience literature to relate the presence and/or absence of RP factors to symptom severity levels (Connor & Davidson, 2003; Oshio et al., 2003). Furthermore, it is consistent with the psychological network literature to compute the number of active symptoms as an indicator of the state of the symptom network (Borsboom, 2017; Cramer et al., 2016). However, symptom levels do not indicate how resilient a system is, as a resilient system should maintain or quickly bounce back to its healthy state despite facing adversity (Kalisch et al., 2017; Rutter, 2012). Thus, resilience entails a low level of symptom activity and robust stability of this low level. Stability measures have been developed in the field of ecology (e.g., see: Beisner et al., 2003; Scheffer, 1990) and physics (e.g., calculating the Gibbs entropy; Jaynes, 1965) and are crucial for studying the resilience of dynamical systems such as ecosystems. In this chapter, we linked concepts from stability theory with existing measures in the resilience literature and psychopathology network theory by proposing to compute the variance of symptom activity patterns as a metric for the *stability* of symptom levels.

Symptom network models including RP factors can have important clinical implications for the analysis of symptom-specific pathways. Symptom network models focus on unique associations between symptoms, which may suggest pathways for which symptom-level intervention strategies can be developed (Blanken et al., 2019). This is especially important for multifactorial disorders such as depression, since scales or sub-scales of these disorders are unstable over time (e.g., they are not measurement invariant), and do not measure one, underlying component (i.e., they are not unidimensional; Fried et al., 2016). Therefore, symptom network analysis offers a promising, novel technique to compare the symptom-specific efficacy of treatment interventions for depression, such as antidepressant medication versus Cognitive Behavioral Therapy (CBT; Boschloo et al., 2019). Including RP factors into symptom networks may yield new insights into symptom-specific pathways involving biopsychosocial factors, which aid the development of novel and more effective intervention strategies.

Apart from analyzing symptom-specific pathways in experimental data, a recent call for "precision psychiatry" urges the development of computational models that integrate data units across scales, such as biomarkers, self-report symptom inventories and clinicians' observations (Fernandes et al., 2017). The collection of experimental data is costly, which is why an exploratory analysis with observational data gives a first indication of possible symptom-specific pathways between specific symptoms and RP factors, such as biomarkers. In this chapter, we showed a simulation-based, exploratory method for observational data, which aims to investigate which symptom-specific pathways might exist with relevant RP factors.

The presented method has some limitations, of which we will discuss the most pressing ones. Using the Ising model as a statistical model to incorporate the theory by Kalisch et al. (2019) has limitations, as the model does not hold for more complex elements of the proposed theory. The first and major one is that the dynamical aspect of the theory by Kalisch et al. (2019) cannot be investigated with the Ising model. The theory states that the presence of a protective factor could, over time, increasingly increment a symptom's threshold, as the protective factor and symptom get entangled in a positive feedback loop. For example, having a job with regular working hours might lead to better sleep and a smaller chance (i.e., stronger negative threshold) to develop the psychiatric symptom insomnia. As sleep improves, one's job performance might also improve, creating a positive feedback loop between the protective factor (stable job) and stronger symptom threshold (insomnia). To investigate this dynamical aspect, an invariant model such as the Ising model is not suitable.

A second limitation is that the Ising model does not consider different time scales on which the various variables operate. It is plausible to assume that a protective factor such as social support evolves on a slower time scale than a psychiatric symptom such

as depressed mood. Future research could expand the proposed system in line with the Personality-Resilience-Psychopathology model (see Chapter 4 in this dissertation) in which personality variables that operate on a slower time scales affect specific network parameters of fast-evolving symptom networks. A third limitation is that the Ising model can only analyze binary data, while measures on symptoms and RP factors will usually be on an ordinal or continuous scale. To address this limitation, our study also provided an empirical illustration of the proposed system using an MGM (Haslbeck & Waldorp, 2020). However, this is not an optimal solution since the MGM also does not account for the dynamical aspect of the theory. Lastly, a limitation of using the Ising model is that specific aspects of its dynamics are restricted within its domain (Haslbeck et al., 2020). Some results from our simulation studies are, therefore, only valid within this specific domain. For example, when using a different binary notation for the state of the variables (the {-1,1} domain instead of the {0,1} domain), increasing the density of the network does not increase symptom activation but only its variance. Dynamics of the {0,1} domain or {-1,1} domain can be translated to each other by transforming the network's parameters as described by (Haslbeck et al., 2020).

We have several concrete suggestions for future research. First, the further development of time-varying models to study holistic models of resilience. Time-varying models allow for dynamic relations between variables over time (Tan et al., 2012). Differential equations describe how variables change as a function of themselves and other related variables, which is why computational models often use these equations to simulate behavioral patterns over time. For example, the computational model for Panic Disorder (Robinaugh, Haslbeck, et al., 2021) explains how panic attacks can instantiate, reach their peak, and end, by using a mathematical model of differential equations. These equations represent dynamic relationships between relevant variables, such as arousal and perceived threat, and are constructed based on reported relationships in the literature. Second, using latent change models such as the Random Intercept Cross-Lagged Panel Model (Mulder & Hamaker, 2020). This model estimates dynamic relations between different variables over time, and could be used to model the effects from RP factors from various domains on psychiatric symptoms. Therefore, future research should focus on collecting longitudinal data, including measures on psychiatric symptoms and various RP factors, and developing and estimating time-varying models.

Second, there are multiple ways in which the proposed metrics, especially SAS, could be improved. As general and straightforward as computing the variance is, it is also not the most exact way of predicting how a system will react in the face of adversity. Furthermore, high variability of a system's behavioral patterns might also be an indicator of strong adaptability (McEwen, 2000). Therefore, computing SAS as a resilience indicator could be further extended by computing a symptom network's sensitivity to *perturbations* (Van Nes & Scheffer, 2015). This would give a more dynamic

indicator of the stability and adaptability of symptom activity patterns when faced with perturbations. Alternatively, when developing a more advanced model for the proposed system in this chapter using differential equations, the system's potential landscape can be computed (e.g., Zhou et al., 2012), giving an exact overview of the system's stable states. This chapter outlined the main reasons for computing ESA and SAS as resilience metrics of symptom networks, while their optimal computation will hopefully be further developed in future research.

Holistic, ecosystem models, including variables from multiple domains such as biopsychosocial models, are an interesting candidate for studying the complex nature of mental health and its relationship with various risk and protective factors. By combining ideas and models from the network perspective of psychopathology (Borsboom, 2017; Cramer et al., 2016; Haslbeck & Waldorp, 2020; van Borkulo, Epskamp, et al., 2014) with the theory on resilience factors targeting network parameters (Kalisch et al., 2019) we took one step forward towards the formalization of resilience.

4

EXTENDING PSYCHOPATHOLOGY NETWORKS WITH FAST AND SLOW PROCESSES

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4.0 ABSTRACT

Network theories have been put forward for psychopathology (in which mental disorders originate from causal relations between symptoms) and for personality (in which personality factors originate from coupled equilibria of cognitions, affect states, behaviors, and environments). Here, we connect these theoretical strands in an overarching Personality-Resilience-Psychopathology (PRP) model. In this model, factors in personality networks control the shape of the dynamical landscape in which symptom networks evolve; for example, the neuroticism item "I often feel blue" measures a general tendency to experience negative affect, which is hypothesized to influence the threshold parameter of the symptom "Depressed Mood" in the psychopathology network. Conversely, events at the level of the fast-evolving psychopathology network (e.g., a depressive episode), can influence the slow-evolving personality variables (e.g., by increasing feelings of worthlessness). We apply the theory to neuroticism and Major Depressive Disorder (MDD). Through simulations, we show that the model can accommodate important phenomena, such as the strong relation between neuroticism and depression, and individual differences in the change of neuroticism levels and development of depression over time. The results of the simulation are implemented in an online, interactive simulation tool. Implications for research into the relationship between personality and psychopathology are discussed.

4.1 INTRODUCTION

Research into the relationship between personality and psychopathology has established that there exist robust associations between personality traits and mental disorders (Kotov, Gamez, Schmidt & Watson, 2010). For example, neuroticism is a well-established risk factor for developing Generalized Anxiety Disorder (GAD; Kotov et al., 2010) and Major Depressive Disorder (MDD; Kendler, Gardner & Prescott, 2002; Kendler, Kuhn & Prescott, 2004); Anti-social Personality Disorder (APD) and substance use disorder (SUD) are related to low levels of agreeableness and conscientiousness (Ruiz, Pincus & Schinka, 2008); and extraversion is negatively related to Social Anxiety (Kaplan et al., 2015).

Several different theories have been put forward to explain how personality and mental health are related. One important answer, sometimes called the vulnerability hypothesis (Ormel et al., 2013), is that personality items measure personality traits and that these personality traits influence the liability to develop disorders. For example, high levels of neuroticism may make an individual more vulnerable to develop MDD, either by directly promoting the processes conductive to developing the disorder or by enhancing the effect of external adverse events that trigger depression. The most important evidence for the vulnerability hypothesis is the prospective correlation between personality and psychopathology, which has been established in several domains, most notably for the personality trait neuroticism and internalizing psychopathology (e.g., MDD, GAD; Saklofske, Kelly, & Janzen,1995; Jylhä & Isometsä, 2006; Fanous et al., 2002).

However, the vulnerability hypothesis is certainly not the only game in town. For instance, Ormel et al. (2013) discuss a number of other pathways through which the statistical association between neuroticism and mental disorders could arise (see also Lahey, 2009): a) via common determinants (e.g., genes), b) because mental disorders are the endpoints of a continuum that, in the low range, captures normal variation in neuroticism (Krueger & Tackett, 2003), and c) because psychiatric disorders themselves increase levels of neuroticism, either permanently or temporarily (Ormel, Oldehinkel, & Vollebergh, 2004; Monroe & Harkness, 2005). Importantly, these explanations are not mutually exclusive: if neuroticism and MDD share part of their genetic background, this does not preclude the possibility that neuroticism induces vulnerability as well; and if the latter is the case, this does not rule out the possibility of permanent negative effects. Distinguishing between these possible scenarios is difficult due to the structural confounding of risk factors and the infeasibility of many interventions that might disentangle the influences of different variables. In fact, it is not clear that it makes sense even to try to distinguish between these scenarios, as each of them may be correct - if only for some individuals some of the time.

Rather than trying to disentangle effects empirically, in the present chapter we approach the problem from the opposite perspective and will propose a modeling framework that allows us to represent all of these different processes in one and the same model. Our point of departure is that of a complexity perspective, in which one could see mental health as an *ecosystem,* meaning that it contains various elements from varying domains, which all interact in order to maintain a healthy balance. In this human ecosystem, a person's cognitions, feelings, behaviors, and environmental features are all in constant interaction with each other (Scheffer et al., 2018). Thus, instead of trying to separate all elements of the system and reducing them to distinct factors, we aim to integrate them into a single theoretical framework. The network approach to psychopathology (Cramer et al., 2010; Cramer et al., 2013; Cramer et al., 2016; Borsboom, 2017) offers a useful starting point for such an approach, because a) it offers a set of formalized models that represents the interaction between different systems, and b) network theories have been proposed both for the etiology and remission of (episodic) mental disorders (Borsboom, 2017; Cramer et al., 2016), and for personality (Cramer et al., 2012). In the network perspective, the question of how to represent the relation between personality and psychopathology thus boils down to the question of how these different networks interact. To answer this question, our central proposal will be to use theoretical and methodological tools from the literature in ecology that deal with the interaction between slow processes (e.g., gradual change of vegetation in an ecosystem over decennia) and fast processes (e.g., monthly fluctuations in the size of populations of insects living on the vegetation; Ludwig, Jones, & Holling, 1978; Rinaldi & Scheffer, 2000). In particular, we propose that the personality network may be primarily understood in terms of a slow process, in which the individual seeks an equilibrium with the environment (Cramer et al., 2012), while the fast process primarily involves the dynamic interactions between symptoms in a symptom network (Borsboom & Cramer, 2013), which in turn feeds back into the slow process.

This chapter is organized as follows. First, we introduce the model wherein personality and psychopathology are both represented. Here, we will shortly describe current network theories of psychopathology and personality and how to integrate these domains, which operate on different time scales, into a single model. Second, we will apply the model to the relationship between neuroticism and MDD. For this purpose, we present a simulation that illustrates the explanatory potential of the model by showing how it represents well-known phenomena in the literature, as well as an interactive online simulation app that allows users to simulate the applied model. We end with discussing the implications of the framework for future research.

4.2 THE PERSONALITY-RESILIENCE-PSYCHOPATHOLOGY NETWORK

Figure 4.1 presents a general schematic overview of the *Personality Resilience Psychopathology network* (henceforth: PRP network). The model represents both psychopathology and personality as complex networks, thus incorporating network theories as have been suggested in the respective literatures (Cramer et al., 2010; Borsboom & Cramer, 2013; Cramer et al., 2016; Borsboom, 2017). The PRP network connects these perspectives by proposing that psychopathology and personality also influence each other; namely, by altering their respective network structures and variables through interactions which take place on different time scales. In the current paragraph, we shortly discuss the relevant network theories, after which we outline a proposal for connecting them.

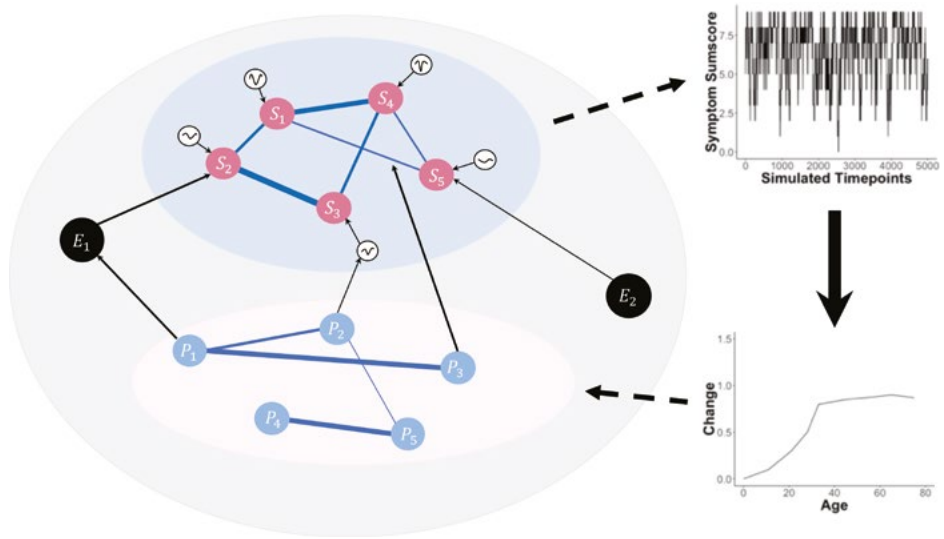


Figure 4.1. The PRP model. The lower system represents a network of personality traits (P1-P5) that co-evolve over periods of years, which is the slow process. The upper system represents a psychopathology network, in which nodes are symptoms (S1-S5) and thresholds are resilience parameters influencing the nodes (represented as dynamical landscapes connected to the nodes). The black nodes (E1 and E2) represent environmental factors. Personality nodes can influence the psychopathology network by shaping threshold parameters or edge connectivity strengths. The personality nodes can also influence the environmental factors, which in turn can influence the psychopathology symptoms directly. The plots on the right represent the dynamics of the processes which operate on different time scales; arrows between the plots indicate the feedback process by which features of the fast network (e.g., a disorder state) influence the variables in the slow network (e.g., stable cognitions or tendencies to display certain affect states).

4.2.1 A network perspective on psychopathology and personality

According to the network perspective (Cramer et al., 2010; Borsboom & Cramer, 2013; Cramer et al., 2016; Borsboom, 2017), psychological constructs such as psychopathology behave as complex systems, in which symptoms of mental disorders directly influence each other. Examples include causal effects of insomnia on concentration problems or fatigue in the case of Major Depressive Episode (MDE; Cramer et al., 2010); the effects of unusual perceptual experiences (e.g., hallucinations in which one sees dead people) on delusions (e.g., the conviction that one has paranormal abilities and is destined to perform particular tasks) in Schizophrenia (Isvoranu et al., 2016); and the effect of obsessions (e.g., the persistent conviction that one is dirty) on compulsions (e.g., powerful urges to respond to the obsession, as through handwashing) in Obsessive Compulsive Disorder. Typically, these complex causal systems are represented in a network structure, where nodes represent the relevant variables (e.g., depression symptoms) and the connections, called edges, represent the direct interactions between these nodes. Such interactions are typically theorized to occur on a relatively short time scale of days to months; an apt analogy is the idea of a set of domino tiles that knock each other over (Borsboom et al., 2011).

A fundamental assumption behind the network perspective on psychopathology is that symptom networks can be characterized in terms of an attractor landscape, in which mental health is a stable state in which no or only a few symptoms are activated (Borsboom, 2017). This attractor landscape controls the dynamic behavior of the system as it reacts to perturbations (Dakos et al., 2015); which could be adverse life events, such as losing a loved one or becoming ill, both of which are known precipitating factors in the development of internalizing disorders (Keller, Neale & Kendler, 2007). In this way, the underlying attractor landscape wherein the network evolves is related to the *resilience* of the network. Psychological resilience refers to the ability to maintain or quickly bounce back into a healthy state after facing some adversity (Werner, 1995; Masten, 2001; Bonanno, 2004; Kalisch et al., 2015; Kalisch et al., 2019; Scheffer et al., 2018). Therefore, if the network structure is such that the healthy stable state is resilient, the system will not enter a prolonged state of persistent symptom activation, but instead quickly recover from perturbations (Cramer et al., 2016; Scheffer et al., 2018). In contrast, individuals that are not resilient are more prone to developing a mental disorder after suffering from a stressful life event. If the network structure is such that the healthy stable state easily collapses into a state of persistent symptom activation, the system is vulnerable (Cramer et al., 2016). Individuals whose psychopathology symptoms are represented in a vulnerable network structure, are more prone to developing a mental disorder after suffering from a stressful life event.

From a network perspective, personality can be viewed as a slowly evolving network structure, which is characterized by the co-evolution of relatively stable cognitions,

affect states, behaviors, and environments (Cramer et al., 2012). Although the fundamental modeling ideas behind network approaches to psychopathology and personality are very similar, symptom dynamics of (episodic) psychopathology usually operate on a shorter time scale (e.g., days, weeks, or months) and as such more naturally lend themselves to the domino-tile metaphor. The evolution of personality, in contrast, may be better thought of in terms of a system of coupled, slowly evolving equilibria (e.g., on a time scale of years or decades). For example, as a person develops the general tendency to participate in social interaction, social skills will co-develop with this tendency in a mutualistic fashion (van der Maas et al., 2006). If a person is generally anxious in social situations, however, the opposite effect will occur. Therefore, this process will be characterized by seeking equilibria with the environment; for instance, it is likely that a more socially skilled individual will seek out an environment that involves a relatively larger degree of social interaction. Similarly, if conscientiousness develops to a larger degree, a person will be more likely to function well in a situation that requires this trait. In this way, individuals slowly "carve out" patterns of characteristic functioning in corresponding environments, and network theory suggests that precisely these stable patterns are picked up in typical personality tests.

The development of stable personality patterns is likely to be subject to both genetic and environmental influences (Boomsma, Busjahn & Peltronen, 2002; Eaves & Eysenck, 1975; Franić, Borsboom, Dolan, & Boomsma, 2014; Kendler et al., 1993) impinging on the development of personality traits (i.e., characteristic dispositional tendencies to experience certain mood states or to act in a particular manner), personality architectures (i.e., coherent sets of interlocking knowledge and appraisal structures; Mischel & Shoda, 1995; Cervone, 2005), and functional relations between elements of the personality structure (Wood et al., 2015). As such, we hypothesize that individuals will display variations in the structure and parameters of the resulting personality networks.

4.2.2 The integration of psychopathology and personality networks

To conceptualize the relation between personality and psychopathology networks we pursue ideas taken from the ecosystems literature, in which this question often arises (Ludwig, Jones, & Holling, 1978; Rinaldi & Scheffer, 2000; Walker, Carpenter, Rockstrom, et al., 2012). In the ecosystems literature, a common way of representing slow-fast interactions is by taking variable values in the slower process (e.g., gradual change of vegetation in an ecosystem over decennia) to affect parameters of the faster process (e.g., monthly fluctuations in the size of populations of insects living on the vegetation). At a given time point, the fast process is then evaluated for its equilibrium, with the variables of the slow process held constant. The fast process is also allowed to have causal effects on the slow process, because properties of the equilibrium distribution of the fast process can influence the values of variables in the slow process (DiFrisco, 2017).

In the current framework, this means that personality traits (which can be viewed as the slow process) operate as parameters of the psychopathology network (which can be viewed as the fast process). Through this mechanism, the slow changing personality traits regulate the *resilience* to external perturbations of faster changing psychopathology symptom networks. However, as the fast process unfolds over time, its properties can also alter certain parameters in the slow process; for example, having a depressed episode can itself change some of the slow changing personality traits (e.g., increasing neuroticism or decreasing extraversion).

Naturally, the distinction between slow and fast processes is not absolute, we do not propose a categorical difference between personality and psychopathology with respect to the time scales at which they operate. Indeed, some personality changes (e.g., learning new coping mechanisms) can be fast with respect to some psychopathology (e.g., slowly evolving negative symptoms of schizophrenia). In addition, some aspects of personality dynamics can operate on a faster time scale (e.g., see Fleeson, 2001; Cervone, 2005; Mischel & Shoda, 1995; Wood et al., 2015). The current approach should not be interpreted as suggesting a fundamental distinction in this respect. However, we do suggest that, in general, the development of personality involves the generation of a relatively stable and coherent pattern of thoughts, affect states, and dispositions to behave in characteristic ways, while episodes of psychopathology typically are seen as reflecting relatively fast processes by which people move into and out of psychopathological states. In addition, for the disorders that show the strongest relations between psychopathology and personality (e.g., consider the relation between neuroticism and depression or anxiety disorders) it appears that the time scales at which the relevant processes operate are in fact different. We discuss the feedback mechanisms of the slow process (i.e., personality) on the fast process (i.e., psychopathology) and the reverse in turn.

4.2.3 Effects of personality (slow network) on psychopathology (fast network)

A central idea in network approaches to psychopathology is that certain network structures make it easier for activation to "spread through" the network. For instance, it has been shown that very strong interactions between symptoms can lead to a situation in which the symptoms sustain each other; a state of consistent symptom activation that we phenomenologically recognize as a mental disorder (Cramer et al., 2016). This directly suggests a way to integrate personality and psychopathology; namely, we can set up a model in which personality traits and their architecture (a) shape the person's psychopathology network parameters and, in doing so, indirectly control a person's resilience to external shocks, and (b) influence the probability of such shocks as emanating from the external field, by predisposing the person to seek out or get caught up in situations that harbor more potential for shocks (see Figure 4.1).

Psychopathology networks are governed by three sets of parameters, each of which may stand under the influence of the personality network. First, symptoms in the psychopathology network have a specific probability of activation, independently of the influence of other symptoms in a network. This probability is represented by their threshold parameters. Second, symptoms are influenced by other symptoms, as represented by their edge weight parameters, which indicate how sensitive symptoms are to activation by their neighbors. Third, symptoms can be activated through events in the external field (the total set of factors outside of the network that impinge on it). Personality factors may affect each of these parameters in characteristic ways.

4.2.3.1 Thresholds

If one peruses personality questionnaires and diagnostic systems, the relation between personality items and psychopathology symptoms immediately stands out. In their meta-analysis, Steel, Schmidt & Shultz (2008) examined 2142 correlation coefficients to study the relationship between subjective well-being and personality. They found strong relationships for many items, over different facets of various personality questionnaires. In fact, this is exactly the feature that generates doubt on whether personality items and psychopathology symptoms measure truly distinct entities. For example, Mõttus (2016) has already argued for a more rigorous examination of the specific causal relationship between overlapping personality traits and psychopathology symptoms, suggesting a holistic and interdependent relationship. This strong relationship between personality items and psychopathology symptoms informs the hypothesis that personality predisposes a person to experience "subthreshold" symptomatology (e.g., see Ormel et al., 2013; Campbell-Sills, Cohan & Stein, 2006). In line with Scheffer et al. (2018) - who propose that nodes in a network can be understood as having their own resilience contributing to the resilience of the network as a whole - personality items could be said to measure properties that affect the threshold parameters of mental health symptoms. This is evident from studying items with content overlap. Taking neuroticism as an example, the items *"I get stressed out easily"* and *"I get upset easily"* (IPIP; Goldberg et al., 2006) may actually assess how easily the GAD symptom *"Restlessness or feeling keyed up or on edge, more days than not for at least 6 months"* (DSM-5; American Psychiatric Association, 2013) will present itself in a person. Therefore, one can hypothesize that a person's score on those two neuroticism items shapes the threshold parameters of the "restlessness" symptom node in a psychopathology network. In the same way, a person's score on the neuroticism item *"I get irritated easily"* (IPIP; Goldberg et al., 2006) asks how easily the GAD symptom *"Irritability, more days than not for at least 6 months"* gets activated (DSM-5; American Psychiatric Association, 2013). Therefore, in a GAD network, this neuroticism item could be said to shape the threshold value for the "irritability" symptom node. Consequently, we propose that personality items affect the resilience of specific nodes, with which they share content overlap, by shaping their threshold values in a psychopathology network. Following this line of reasoning,

content overlap is thus no longer a validity threat, but instead an asset that can be exploited to inform models better.

4.2.3.2 Connections

A second way in which the slowly evolving personality factors can affect resilience is by altering the connectivity of the symptom network (Cramer et al., 2012). For instance, while it may simply be a feature of the human system that insomnia causes fatigue, the strength of this relationship plausibly may depend on a host of factors, which include those in the realm of personality (Blanken et al., 2019). Similarly, while feelings of worthlessness may cause suicidal ideation for many individuals (Williams et al., 2006), the degree to which one is prepared to engage in suicidal ideation plausibly depends on one's personality constitution.

In previous work on network approaches to personality (Cramer et al., 2012), connectivity of the symptom network was in fact suggested to be the way in which neuroticism could be operationalized in a network model for MDD. Although this intuitively sits well with the idea that neuroticism has to do with the reactivity of the system (e.g., in the form of psychological reactions to stress; Kendler, Kuhn & Prescott, 2004), the actual content of current operationalizations of neuroticism in personality questionnaires primarily formulates very general tendencies for feelings of worthlessness, anxiety, or depressed mood. We suggest that current operationalizations of neuroticism may therefore better be considered to assess threshold parameters of feelings of worthlessness, anxiety, or depressed mood, as they appear to concern not only reactivity to other symptoms but also reactivity to the external field.

With respect to the relation between thresholds and connectivity, it should be noted that these properties are in part communicating vessels: if one's symptom thresholds change, this has direct implications for the effective connectivity within the symptom network, as a more resilient symptom will ceteris paribus require more activation and thus stronger connections in order to be activated. Similarly, if one has two symptom networks with equal positive connectivity parameters in, for example, an Ising model (Marsman et al., 2018), then these need *not* be equally resilient; if the thresholds are different, then the network with higher thresholds will be less resilient. It should be noted that current tests for differences in symptom connectivity (van Borkulo et al., 2015) do not account for differences in thresholds and thus should not be mistaken for tests of resilience. How to separate these effects from each other is an important question for future methodological research.

4.2.3.3 The external field

Personality involves a general tendency to engage in certain types of interactions (Magnus, Diener, Fujita & Pavot, 1993; Ozer & Benet-Martinez, 2006; Soto, 2019).

For instance, extraverts are in part defined as people who seek out social situations (Ashton, Lee & Paunonen, 2002), and conscientious individuals are more often found in more demanding job situations (Ng, Ang & Chan, 2008). As the probability of events that may impinge on the symptom network are not likely to be equally distributed over these situations, it follows that personality may also influence the likelihood of relevant events in the external field. For example, as extraverts are more likely to settle in jobs that involve social interaction, any systematic effect of social interaction on psychopathology symptoms would be amplified for them. To the extent that personality factors are subject to genetic influences, this mechanism may in part explain the fact that environmental features (possibly including adverse life events) appear to be associated with genetic factors (Kendler & Baker, 2007; Krapohl et al., 2017).

4.2.4 Effects of psychopathology (fast network) on personality (slow network)

As the slow process of the personality network unfolds, certain states of the psychopathology network can become more likely. Importantly, however, these states can also feed back into the slow process. This may either increase the vulnerability of the psychopathology network or increase its resilience. These two categories of effects are referred to as *scarring* (Ormel et al., 2013; Monroe & Harkness, 2005) and *steeling* (Rutter, 2012a; Rutter, 2012b).

4.2.4.1 Scarring

It is possible that experiencing a mental disorder induces changes in the slow personality network, which alter that network in such a way as to reduce the resilience of the person to adverse events. This feature is known in the psychopathology literature as a *kindling effect* (Kessler & Wang, 2009). For instance, in the literature on depression, such effects have been repeatedly suggested (Hammen, Mayol, de Mayo & Marks, 1986; Monroe, Rohde, Seeley & Lewinsohn, 1999). In these accounts, the amount of stress or adverse life events necessary to trigger the onset of the first Major Depressive Episode (MDE) is hypothesized to be higher than the amount of stress that triggers its recurrence (Monroe & Harkness, 2005). In other words, once a person has suffered from an MDE, he or she is more likely to have recurrent MDEs, even to the point that an MDE may develop in the absence of any triggering events (Monroe, Anderson & Harkness, 2019).

This effect implies that the way the depression network *reacts* to stressors has changed once it has been in a depressed state. From our perspective, this suggests the hypothesis that the fast process (the MDD symptoms) feeds back into the slow process (the personality traits). That is, once a person has suffered from an MDE, this experience can in itself change the personality elements of the system (which then, in turn, lowers the resilience of the depression network). For example, the experience of

an MDE may fuel the idea that one has failed in life, thereby increasing the tendency to experience feelings of worthlessness – a personality variable in the slow network. However, the effect might also be moderated via the external field: once the network is pulled into a disorder state because of a life event, it might react different to future (minor) stressors since it has now shifted towards a different attractor basin. In other words, its equilibrium state is now changed to a disorder state, making it easier (i.e., less activation from the external field is necessary) for the MDE to recur.

4.2.4.2 Steeling

Another example of how the interaction between the different fields in our model might explain real-world phenomena from clinical practice, is the steeling effect (Rutter, 2012b). The steeling effect entails the idea that resilience is built up through successful responses of the system to adverse events, which in themselves strengthen the resilience of the system. Thus, the steeling effect is the mirror image of the scarring effect.

Steeling effects are often observed in biological systems. The classic example is the human body building up resistance to viruses if injected by a small dosage of pathogens. Just like resistance to infections is induced by administering a small and modified dose of the pathogen in the body, thereby strengthening the immune system, resilience of mental health may arise from an increasing ability to cope with adverse life events after successfully having went through other adversities in the past (Rutter, 2012b). One way in which this may happen occurs when the experience of an episode of a mental disorder leads people to inquire new insights about themselves (e.g., through psychotherapy) that may allow them to increase their skills in dealing with adverse life events. Another example involves people who have experienced episodes of psychosis or depression and have learned to increase their resilience by setting up (social) early warning systems that may alert themselves and their environment to impending escalations of the system (Elder, 1974; Luthar, Cicchetti & Becker, 2000; Troy & Mauss, 2011). Finally, a recent study found that an early career set-back (namely, falling just below the threshold for receiving a research grant) actually had a positive impact on the future career of junior researchers (Wang, Jones & Wang, 2019). Thus, the steeling effect entails that successfully surpassing adversity (meaning that there might be some temporary psychopathology symptom activation, but no development of a full-blown mental disorder) increases resilience.

In our model, this is represented as follows: when the psychopathology network structure is resilient, the fast process changes the variables in the slow process (personality network) which share content overlap, so as to increase resilience. In the next section, we apply the theoretical PRP model to neuroticism and MDD, showing how the scarring and steeling effects can be simulated.

4.3 APPLICATION: THE RELATIONSHIP BETWEEN NEUROTICISM AND MDD

To illustrate the proposed framework, we apply the PRP model to the relationship between neuroticism and MDD. Figure 4.2 shows the applied model: the center network represents the slow process of personality, and the network at the border represents the fast process of MDD. We propose that the slow process of neuroticism influences the development of MDD by altering the depression symptom network structure. We hypothesize that certain neuroticism items assess properties that affect the thresholds of depression symptoms; in particular, this occurs when a neuroticism item asks about a general tendency to display the states that define the corresponding MDD symptom. We refer to these neuroticism items showing content overlap with certain MDD symptoms as "overlapping items".

The exact nature of the relationship between MDD and neuroticism remains an open question, which could have multiple answers. For example, one could say that there is a causal relationship, or a constitutive relationship. However, in order to provide concrete steps for the simulations, this relationship between the MDD symptom thresholds and neuroticism items needs to be specified. We propose that there is a supervenience relationship between the overlapping neuroticism items and the MDD threshold values. Supervenience is defined as follows: "A property X can be said to supervene on lower order properties Y if there cannot be X-differences without Y-differences. Thus, the presence of Y-differences is a necessary (but insufficient) condition for the presence of X-differences" (Kievit et al., 2011, p. 70). This allows for multiple realizability, for example where different item scores might lead to the same sum score: there cannot be a change from the sum score of 8 to a sum score of 9 without there also being changes in the item scores, but a sum score of 8 can be the result of the item scores of 4 and 4, 3 and 5, 2 and 6, etcetera.

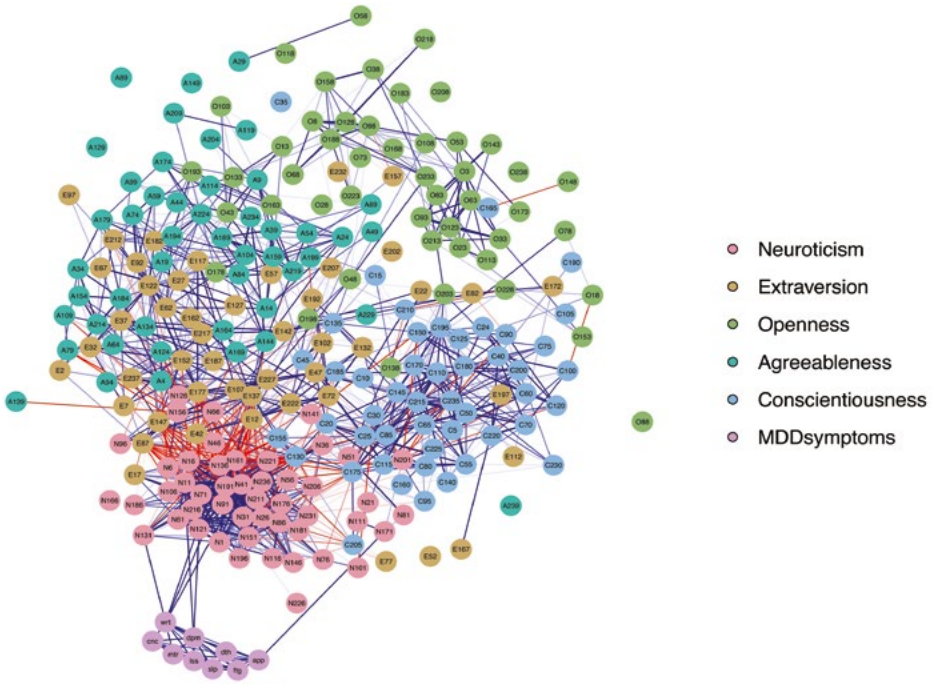


Figure 4.2. The applied PRP model to an example of neuroticism and depression. The center network represents the slow process (the personality elements) and the network at the border represents the fast process (the depression symptoms). The MDD symptoms are: depressed mood, loss of interest, appetite disturbance, sleep disturbance, psychomotor agitation, fatigue, feelings of worthlessness, concentration problems and thoughts of death. The MDD symptoms and neuroticism items which share content overlap are connected in the figure. In this way, one can imagine various mental disorder symptoms interacting with various personality factors.

In our model, the MDD symptom thresholds supervene on the lower order personality items: differences in neuroticism item scores are a necessary but insufficient condition for differences in MDD threshold values. There cannot be differences in the threshold values without there also being a difference in the item scores, but there *can* be differences in the neuroticism item scores without altering the threshold values, because the changes in the neuroticism item scores can cancel each other out.

4.3.1 Phenomena to be accommodated

We identify three important phenomena regarding the relationship between MDD and neuroticism that are well established in the literature, and show how the applied PRP network model accounts for them in a simulation: 1) the strong correlation between MDD and neuroticism in the general population 2) the fact that this correlation remains relatively strong for the rest scores and 3) Individual differences in the effect of stressful life events (SLEs) on depression and neuroticism.

4.3.1.1 Strong correlation between MDD and neuroticism

A widespread finding in the literature regarding the relationship between MDD and neuroticism is their strong correlation in the general population: Jylhä & Isometsä (2006) report a correlation of $r = .71$ (N = 441) between neuroticism and depression symptoms, Fanous et al. (2002) report a correlation of $r = .68$ for males and $r=.48$ for females (N=3771). Thus, our model should show a similar result. Since the model iterates over time, in which the fast and slow processes influence each other and are therefore updated with every iteration, we expect that the correlation between MDD and neuroticism increases with every iteration.

4.3.1.2 Robustness against removal of overlapping item

It is a well-known phenomenon from the literature that the strong correlation between neuroticism and MDD and GAD holds after removing the neuroticism items that have content overlap with the psychopathology symptoms (Walton, Pantoja, and McDermut, 2018; Brandes et al., 2019). From a latent variable model perspective, this can be explained by stating that the overlapping items and symptoms are only indicators of the underlying, correlating factors neuroticism and MDD or GAD. This phenomenon of the robustness of the rest-score correlation is therefore used as an argument in favor of the latent variable approach, stating that the correlation between the neuroticism items and MDD or GAD cannot merely be a product of tautologies (Walton, Pantoja, and McDermut, 2018; Brandes et al., 2019).

However, our model could provide an alternative explanation for the phenomenon of the robustness of the correlation between neuroticism and MDD after removing the overlapping items. In the current simulation setup, the sole point of contact between the neuroticism network and the MDD network lies in the three symptoms whose threshold is altered slightly as a function of the seven corresponding personality items. If the true data-generating mechanism is similar to the PRP model, then the correlation between non-overlapping neuroticism scores and non-overlapping depression symptoms will arise as a matter of necessity. The reason is that even though only a subset of the neuroticism items is connected to the MDD symptoms, individual differences in these items are nevertheless positively correlated with non-overlapping neuroticism items. For example, thoughts of death and loss of interest could be present due to direct activation by depressed mood and feelings of worthlessness, which could have been activated by the corresponding neuroticism aspects. Therefore, the non-overlapping neuroticism items will be correlated to the MDD symptoms. At the same time, non-overlapping MDD symptoms will "inherit" the effects of neuroticism on the overlapping symptoms. Through this mechanism, non-overlapping MDD symptoms will get correlated to neuroticism. As a result, all MDD symptoms are correlated to all neuroticism items in the end. This means that because the data were generated with all variables, the non-overlapping variables were affected by and/or affected the overlapping variables, thereby causing the non-overlapping MDD and neuroticism variables to get correlated.

In order to test if the robustness of the rest-score correlations between neuroticism and MDD arises from the simulations of our PRP model, and to test if this is due to our proposed data-generating mechanism, the simulations should show two results:

If the overlapping neuroticism items and symptoms are removed from the data-generating mechanism, meaning that there is no point of contact between the neuroticism network and the MDD network, the correlation between neuroticism and MDD should approach zero. This can be tested by setting the scaling factor between the overlapping items and MDD symptom thresholds to zero and calculating the correlation between MDD and neuroticism after one iteration of the simulation.

If the overlapping neuroticism items and symptoms are present in the data-generating mechanism, but removed from the rest-score correlation calculations (as is done in studies such as Walton, Pantoja, and McDermut, 2018), the correlation between the MDD symptoms and neuroticism items should be robust against the removal of the overlapping item-symptom variables in the simulated data. This can be done by simulating the data according to the proposed PRP model, and then calculating the rest-score correlations between the MDD symptom sum score and the neuroticism item scores, without the overlapping items.

4.3.1.3 Individual differences in the effect of SLEs on depression and neuroticism

Individuals' levels of neuroticism change over time (Costa et al., 1986; Steunenberg et al., 2005), and this change seems to be driven by stressful life events (SLEs). After suffering from SLEs, levels of neuroticism are likely to increase (Riese et al., 2013), which, in turn, increase the probability of developing depression (Saklofske, Kelly & Janzen, 1995). People who have been diagnosed with an MDD once, are not only more likely to suffer from another depressive episode again, but have also been found to have an increased level of neuroticism (Bolger & Zuckerman, 1995). On the other hand, individuals who show resilient coping mechanisms, are less depressed after being exposed to significant trauma, despite controlling for levels of neuroticism (Sinclair, Wallston and Strachan, 2016). Also, Roberts et al (2017) found in their meta-analysis of 207 studies that emotional stability (which entails a low score on neuroticism) was the primary trait domain showing positive changes after psychotherapeutic interventions. Our model accommodates for these individual differences (Monroe & Harkness, 2005; Monroe & Harkness, 2019) by proposing that an individual's resilience against developing MDD affects their level of symptomatology and neuroticism, via either scarring or steeling effects. Note that resilience is not conceptualized as a static trait, but as a global characteristic that supervenes on the MDD network structure. In other words, resilience is not a node in an individual's network, but a characteristic of the network structure itself.

4.3.2 Simulation

In this simulation we connect an empirically estimated MDD network with an empirically (independent) estimated neuroticism network. All the simulations are executed in *R* (R Core Team, 2013).

To translate the above ideas into a formalized computational model, we need to choose a model structure to inform the dynamics and interaction between neuroticism and MDD symptomatology. Ideally, such models would be based on data gathered and analyzed in a longitudinal prospective study that both contained sufficient repeated personality assessments to estimate the parameters of the slow process, and tracked MDD symptomatology using intensive time series data as people moved in and out of major depressive episodes. To the best of our knowledge, neither such data nor statistical models to analyze them with respect to the interaction between fast and slow processes currently exist in the context of (noisy) psychological data. Therefore, we have chosen to use two models that have been proposed to capture some of the structure (and, in the case of MDD, also some of the dynamics) of personality and MDD: we use the MDD simulation model proposed by Cramer et al. (2016) and connect it to the personality network proposed by Cramer et al. (2012). Importantly, the current modeling study aims to establish that the proposed theory *can* explain important phenomena in the relation between MDD and neuroticism; it is not intended as a fully realistic model of this interaction and should not be interpreted as such. Thus, the simulations have the limited but nevertheless important aim of establishing a proof-of-possibility.

4.3.2.1 Data

For the neuroticism network we use the "big5" dataset as inventory as incorporated in the R-package *qgraph* (Epskamp et al., 2011). The dataset contains the measurements of a Dutch translation of the NEO PI-R (Costa & McCrae, 1992) on 500 first year psychology students (Dolan, Oort, Stoel, Wicherts, 2009). There are 48 neuroticism items, which will all be used in our simulation. For the MDD network, we use the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD) dataset (Kendler, Karkowski & Prescott, 1999). The participants are 8973 twins from the Mid-Atlantic Twin Registry. The MDD symptoms are measured during a psychiatric interview using an adaptation of the Structured Clinical Interview for DSM-III-R (Spitzer & Williams, 1992), where each participant was asked if they had experienced any of the 14 disaggregated DSM-III-R symptoms. The dataset contains binary data on the presence/absence of 9 aggregated symptoms of MDD (criterion A for MDD in DSM-III-R; American Psychiatric Association, 1987). The symptoms are aggregated following recommendations as made in Aggen, Neale & Kendler (2005) and following the criteria in the DSM. Table 4.1 shows the relation between the (dis)aggregated symptoms and the DSM criteria for MDD.

Table 4.1. Aggregated/Disaggregated criteria for MDD and the DSM symptomatology.

(Dis)aggregated criteria	DSM Symptom criteria
(1) Depressed mood	(1) Depressed most of the day, nearly every day
(2) Markedly diminished interest	(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
(3a) Significant weight loss or (3b) Significant weight gain or (3c) Increased appetite or (3d) Decreased appetite	(3) Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
(4a) Insomnia or (4b) Hypersomnia	(4) Insomnia or hypersomnia nearly every day
(5a) Psychomotor agitation or (5b) Psychomotor retardation	(5) Psychomotor agitation or retardation nearly every day
(6) Fatigue or loss of energy	(6) Fatigue or loss of energy nearly every day
(7) Feelings of worthlessness	(7) Feelings of worthlessness or excessive or inappropiate guilt nearly every day
(8) Inability to concentrate	(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day
(9) Recurrent thoughts of death.	(9) Recurrent thoughts of death, recurrent suicidal ideation or suicide attempts

Table 4.2 shows the hypothesized relationships for these two sets of variables, based on the content of the items. This means that we hypothesize that there are seven NEO PI-R items which have content overlap with three MDD symptoms.

Table 4.2. Hypothesized relationships for the PRP network model applied to neuroticism and MDD.

Neuroticism item	→	MDD symptom threshold
N11: "I often feel lonely or sad" (*) N71: "I seldom feel sad or depressed"	→	"Depressed Mood"
N161: "I have a low opinion of myself" N131: "I easily blame myself when something goes wrong" N136: "I often feel inferior to others" N41: "I sometimes feel completely worthless" (*)	→	"Feelings of Worthlessness"
N171: "Sometimes I eat until I feel sick"	→	"Appetite Disturbance"

Items with an (*) are asked in a contra-indicative fashion in the original questionnaire (e.g., N11: "I seldom feel lonely or sad"). The raw data are already recoded.

For illustrative purposes, Figure 4.3 shows the applied PRP model with a subset of the 48 neuroticism items, in order to show how the overlapping MDD symptoms and neuroticism items are connected to each other in the simulation.

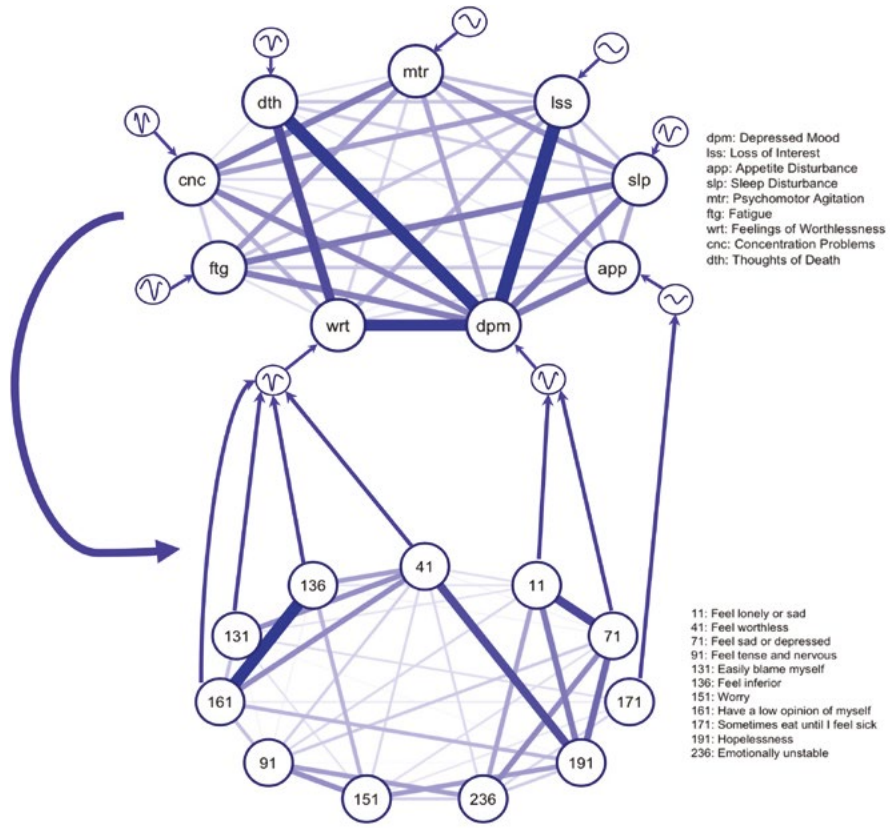


Figure 4.3. The applied PRP model to neuroticism and MDD. Relations between NEO PI-R neuroticism items (Costa & McCrae, 1992) and thresholds of MDD-symptomatology as based on the correspondence between the content of the items. The upper network represents an MDD network, the lower network represents a neuroticism network. For illustrative purposes, only a small subset of the 48 neuroticism items is represented here, including the seven neuroticism items that are hypothesized to alter several MDD threshold values. A neuroticism item is connected to the threshold of an MDD symptom if the item formulates a general disposition to experience a phenomenon identified by a symptom. For instance, the disposition assessed through the item "Sometimes I feel completely worthless" is taken to influence the threshold of the DSM-5 symptom "Feelings of worthlessness or excessive or inappropriate guilt, nearly every day for at least two weeks".

The Ising model (van Borkulo et al., 2014) was used as a prototype model for the organization and dynamics of an MDD symptom network, which represents the fast process. The Ising model is a straightforward model for binary (i.e., absent or present) symptoms that implements symmetric pairwise interactions. Although the Ising model is a toy model rather than a fully realistic model of symptom interactions, it is helpful as a simplest non-trivial case: its behavior is sufficiently simple to be mathematically tractable, and at the same time sufficiently rich to represent important phenomena in

the etiology of mental disorders, such as alternative stable states, critical transitions and hysteresis (van Borkulo et al., 2014; Cramer et al., 2016; Marsman et al., 2018). The Ising model is characterized by two parameters: a threshold parameter for each node (e.g., MDD symptom) in the network and a connectivity parameter for each edge (e.g., the connection between two symptoms). The threshold of a node represents the autonomous disposition of the node to be present and, thus, reflects the probability of being present in the absence of any influences of connected nodes. The connectivity parameter for each edge represents the strength of two nodes influencing each other. The parameters of the Ising model can be estimated with node-wise logistic regression, in which the intercept is an estimate of the threshold and the slope is an estimate of the edge strength. In addition, the model evolves in an external field (i.e., any factor outside the model, such as stressful events) that influences the node states.

The neuroticism network is estimated with a Gaussian Graphical Model using LASSO regularization (GGM; Epskamp et al., 2018), and represents the slow process. The GGM handles continuous data, which is suitable for the 5-point likert-scale items of the NEO PI-R dataset. LASSO regularization limits spurious edges, meaning that the estimated model is less likely to contain false positive connections (Epskamp & Fried, 2018).

Now there are two empirically estimated networks representing neuroticism and MDD. These are cross-sectional networks, meaning they are estimated from the differences between individuals. However, we assume that the estimated networks can be used as a blueprint for all individuals. To make sure we have enough power for our simulations, we use the estimated network parameters to simulate 1000 participants using the *ggmGenerator* function from the *bootnet* R-software package (Epskamp, Borsboom & Fried, 2017). To make explicit that we are analyzing data of simulated individuals, we will refer to these simulated individuals as "sims". With these neuroticism scores, our simulation study begins.

Sims differ in the starting point of the simulation. That is, they differ on their neuroticism item scores, which are generated according to the empirically estimated network structure. For each sim, the networks communicate as shown in Figure 4.3. The sim's overlapping neuroticism score is, thus, connected to the MDD network parameters. This works as follows. For every iteration, both the neuroticism and MDD networks influence each other: every sim's neuroticism item scores will affect their MDD network structure (by altering the relevant MDD symptom thresholds), which results in an altered level of resilience. Every sim's own resilience against developing MDD then affects their neuroticism item scores at the next iteration of the model. Thus, even though this application of the PRP network model is derived from cross-sectional data, we simulate individual-level dynamics in order to generate hypotheses regarding personalized trajectories over time. Next, we describe the simulation process in more detail.

4.3.2.2 Simulating the fast process

From the PRP model it follows that neuroticism items that have content overlap with depression symptoms should influence the threshold values of the respective symptoms. This is modeled as follows: 1) all neuroticism item scores are standardized for all sims, 2) standardized item scores of the neuroticism traits that we hypothesize to alter a certain MDD symptom (see Table 4.2) are summed, 3) multiplied by a scaling factor that represents the influence of neuroticism on MDD (in our case, we use a scaling factor of 0.1), and 4) added to the MDD threshold of the focal MDD symptom. For example, to compute the novel threshold value of the sims's MDD node "Feelings of Worthlessness" on each iteration, the standardized scores on the neuroticism items "N41: I sometimes feel completely worthless" , "N131: I easily blame myself when something goes wrong", "N136: I often feel inferior to others" and "N161: I have a low opinion of myself" are summed, multiplied with a scaling factor (in our case .1), and added to the participant's original MDD symptom "Worthlessness" threshold value. This is repeated for every MDD symptom that is expected to be influenced by neuroticism items. Then, the MDD network parameters are updated for every individual, based on their neuroticism item scores. This is done on every iteration, thus, the thresholds of the focal MDD symptoms are updated based on their value on the previous iteration.

Glauber dynamics (Glauber, 1963) are used to simulate timepoints from our PRP network, in order to study the influence of neuroticism on the depression network. This process operates as follows. For every time point, the algorithm selects one randomly chosen MDD node. This node can be active (encoded by a "1") or inactive (encoded by a "0")[5]. Subsequently, the state of this node gets temporarily flipped, meaning that an active (inactive) node gets deactivated (activated). Then, the current and flipped state are compared with each other, and the likelihoods of the resulting system states are compared. On the basis of this evaluation, the most probable state for the relevant node is chosen for the next time point, based on the state of all other nodes, taking the network architecture into account. As a result, the most likely trajectory of the depression network can be simulated, mimicking a continuous process. Figure 4.4 shows an example of an individual's simulated dynamics using Glauber dynamics.

By simulating the evolution of the system in this manner, we can study the dynamics that are implied by any given network structure. Of course, the veracity of these dynamics depends on the degree to which the Glauber dynamics approximate the actual process operative in the etiology of MDD. Since this is unknown at the moment,

5 Following the suggestions as made in Haslbeck, Epskamp, Marsman & Waldorp (2020), we use the transformed {0,1} parameters of the Ising model to compute the Glauber dynamics.

this model should primarily be seen as a first approximation that allows us to model the process. However, as science progresses and more information about the relevant etiological processes becomes available, the current model can straightforwardly be adapted according to new scientific insights.

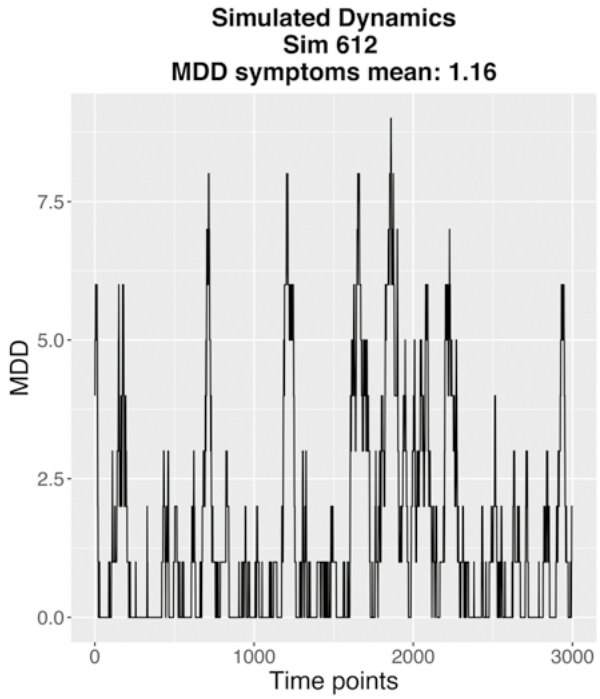


Figure 4.4: An example of simulated dynamics of the fast process. The example shows the dynamics for one simulated participant (sim 612). The x-axis shows the time points, the y-axis shows the sum score of the active MDD symptoms. This participant shows a sum score of 0 - 2 active MDD symptoms most of the time, but there are also some peaks leading to more than 5 active symptoms. However, these peaks are episodic and the participant does not get 'stuck' in the depressed state (i.e., this sim seems to recover).

4.3.2.3 Simulating the slow process

For every iteration of the model, the sim's fast process affects their slow process.[6] If a person has a vulnerable MDD network structure and is therefore more likely to suffer from a depressive episode, this can have a scarring effect. We account for this in our simulation by slightly increasing certain neuroticism item scores (we increase the standardized overlapping scores with 0.3) in the next iteration of the model. This

6 We want to note that in our simulation study, we model the influence of the fast process (MDD) on the slow process (neuroticism) but do not let neuroticism evolve over time. That is, in our simulation model, the effect of the depression symptoms on the overlapping neuroticism indicators does not spread through the neuroticism network.

will, in turn, affect the thresholds of certain MDD symptoms (see Table 4.2), making them more vulnerable and therefore more likely to suffer from a depressive episode. We follow the opposite procedure for a sim with a strongly resilient network structure. This sim is unlikely to suffer from a major depressive episode despite facing adversity, and therefore we lower the relevant neuroticism item scores on the next iteration of the model (we lower the standardized overlapping item scores with 0.3). This will implement the steeling effect, since this sim is more likely to also have a more resilient network structure because of the lower neuroticism level.

Naturally, not every resilient individual will always show steeling effects, since steeling effects are more likely to occur within highly resilient individuals who successfully surpass adversity (Rutter, 2012b). Therefore, we also consider the individuals who show moderate resilience, which show no further change (Masten, 2001; Bonanno, 2004). In our simulation, sims with moderate resilience will show no scarring nor steeling effects in the next iteration of the simulation, meaning their neuroticism scores stay the same for the next iteration.

To assess the resilience of the MDD network structure, we again simulate Glauber dynamics but add an artificial "shock" to the system by forcing all nodes to be active for one time point. This allows us to see how the system bounces back from these short but intense perturbations, representing an SLE. Then, dynamics with and without the perturbations are compared and the resilience of the system can be quantified[7].

We can now iterate the whole model simulating both the fast and slow process at every iteration. The strength of the relationships between the fast and slow processes can be altered to study the effects of different levels of feedback between the slow and fast network processes. That is, we can alter how strongly the neuroticism items affect the MDD symptom threshold values and how strongly the resilience of the MDD network influences the neuroticism item scores at the next time point by altering the scaling factor. We have developed an interactive simulation tool for users to replicate our simulations with different values of the scaling factor, to study its impact on the influence of the slow and fast processes. This simulation tool can be found at: https://gabylunansky.shinyapps.io/PRPmodel/.

4.3.3 Results

4.3.3.1 Strong correlation between MDD and neuroticism

The first phenomenon that should follow from the applied model is the strong correlation between MDD and neuroticism. Figure 4.5 shows how the correlation

7 This is quantified with a resilience indicator that measures the degree to which the system is susceptible to shocks. See the supplementary materials for the computations.

between the MDD symptom sum scores and neuroticism item scores increases across the three iterations of the model with a scaling factor of 0.1: from *r*=.41, to *r*=0.59 and *r*=0.66. Importantly, this means that small influences of the processes on each other, which arise only from the contact points between the seven neuroticism and three MDD networks (Figure 4.3), are able to generate strong correlations between the total scores computed on these networks.

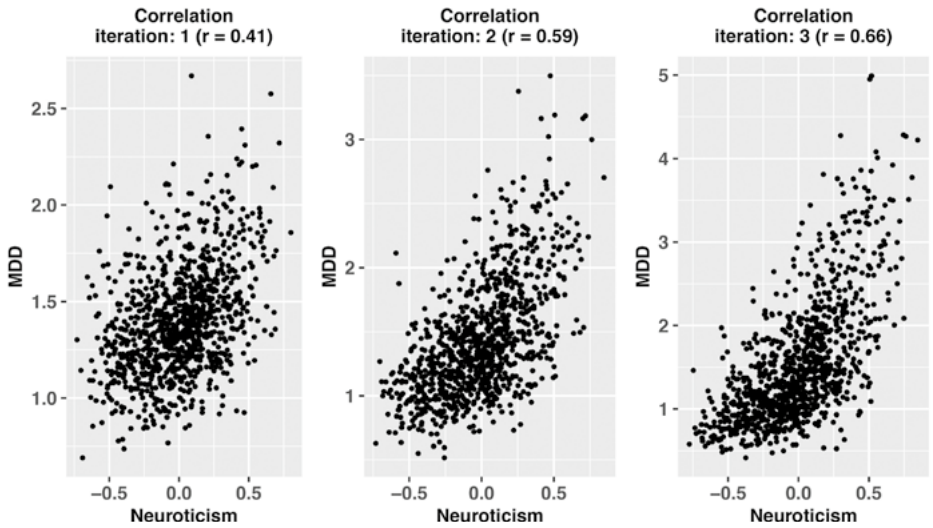


Figure 4.5. The increasing correlation between MDD and neuroticism. On the x-axis are the standardized neuroticism item scores, and on the y-axis are the mean MDD symptom sum scores. The data are generated with a scaling factor of 0.1. As the PRP model iterates, meaning that both the fast and slow processes influence each other, the correlation between neuroticism and MDD increases.

4.3.3.2 Robustness against removal of overlapping items

Next, we investigated whether the proposed model can demonstrate the strong correlation between MDD and neuroticism, even after removing overlapping MDD symptoms and neuroticism items from both the *data-generating mechanism* and the *computations of the rest-score correlations from the simulated data*.

First, to remove the overlapping MDD symptoms and neuroticism items from the data-generating mechanism we implemented a simulation wherein both neuroticism and depression are scaled to have no effect on each other. In other words, all the arrows in Figure 4.3 from the neuroticism items to the MDD symptom thresholds and from the MDD network to the neuroticism item scores are set to zero (scaling factor = 0). Since, in this case, the dynamic processes on the networks are independent, there should be no relationship between MDD and neuroticism across all iterations of the simulation. As the scaling factor increases, however, the feedback between the networks should

increase and the correlation between MDD and neuroticism should get stronger as a result. Figure 4.6 shows that this is the case: the correlation for the simulation with a scaling factor of 0 is *r* = .01, as expected, but when the scaling factor increases to .05 or .1, the correlation between MDD and neuroticism is respectively *r*=.21 and *r*=.41 for the first iteration (i.e., the first round in the simulation in which the neuroticism and MDD network affect each other).

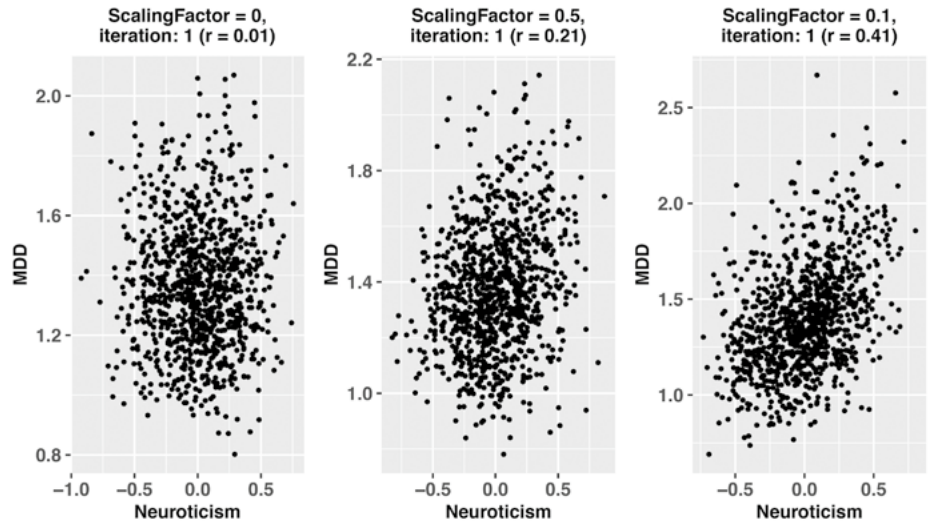


Figure 4.6. The correlation between MDD and neuroticism for different scaling factors. On the x-axis are the standardized neuroticism item scores, on the y-axis are the expected values of the MDD symptoms. On the left panel the scaling factor of the PRP model is zero, meaning that there is no relation in the data-generating model between neuroticism and MDD. In the middle panel this scaling factor is set to 0.5, and in the right panel to .1. The correlation increases with the scaling factors.

Second, to check the robustness of the rest-score correlations after removing the overlapping items from the simulated data, we simulated data with the PRP model (i.e., including overlapping items) with scaling factor = 0.1 and simulated data for three iterations. This resulted in three datasets including overlapping items. Figure 4.7 shows what happens if we calculate the correlation between simulated neuroticism and MDD data after removing the overlapping items in the same way as has been done in the literature to test the effects of item overlap (Walton, Pantoja, and McDermut, 2018). Next, we computed the mean rest-scores of MDD and neuroticism for each individual and correlated those scores. The rest-score correlations over the three iterations are respectively: *r*=0.3, *r* = 0.41 and *r* = 0.43. As Figure 4.7 evidences, the resulting correlation between the rest-scores after removal of overlapping items is only slightly weaker than the correlation between the total scale scores. Clearly, the correlation between neuroticism and MDD is robust against removal of overlapping items.

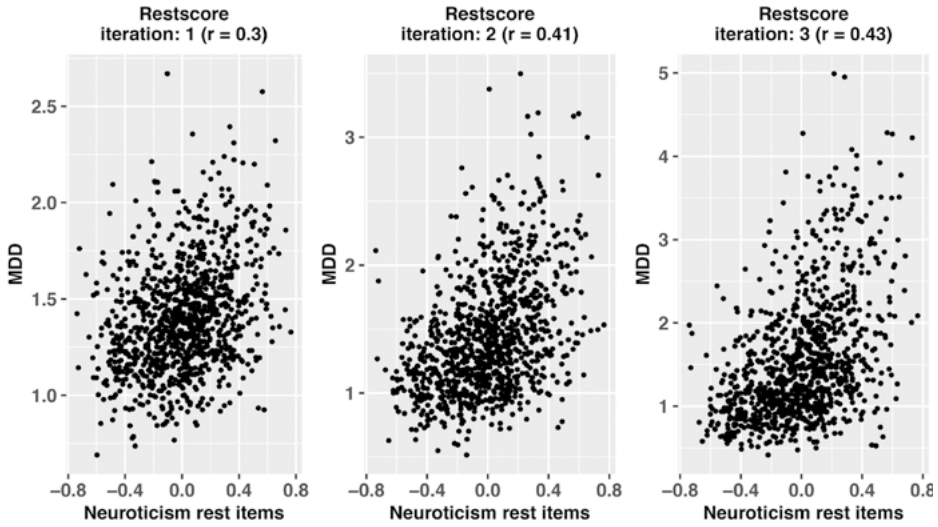


Figure 4.7. The rest-score correlation between MDD and neuroticism. Removal of the overlapping items from the rest score calculation. On the x-axis are the standardized neuroticism item scores that have no overlap with the MDD symptoms, on the y-axis are the mean MDD symptom sum scores. The data are generated with a scaling factor of 0.1. The correlation of the rest scores between neuroticism and MDD increases over the iterations of the PRP model.

4.3.3.3 Individual differences in the effect of SLEs on depression and neuroticism

To facilitate the presentation of these results, we categorized simulated individuals into three groups: sims that always show the steeling effect (i.e., across all iterations of the model their depression network is resilient and thus their neuroticism score lowers), sims that always show the scarring effect (i.e., across all the iterations of the model their depression network is vulnerable and thus their neuroticism score increases), and sims that show a combination or neither of these effects (i.e., across all iterations the depression networks are sometimes resilient and sometimes vulnerable; therefore, sometimes their neuroticism items might increase or decrease, but most of the times their neuroticism item scores will remain the same).

Figure 4.8 shows individual trajectories of three randomly selected sims, each from a different group, to show scarring effects, steeling effects, or neither of these effects. For instance, sim 182 showing scarring effects, shows sudden jumps into a disorder state (where the sum score of activated symptoms is > 5), and stays in that state for a relatively prolonged time. This dynamic increases over the iterations, since the vulnerable network structure leads to a higher neuroticism item score, which in turn negatively affects their MDD network structure. On the contrary, sim 360 shows steeling behaviour: there is spontaneous recovery after short peaks of an increased sum score of MDD symptoms, and as the model iterates, the participant shows no symptom activation for most of the time and less peaks. Lastly, sim 14 shows no clear

scarring or stealing behaviour. This means that this sim sometimes shows moderate vulnerability when facing an SLE, and at other times moderate resilience, without a clear pattern or changes in the level of neuroticism.

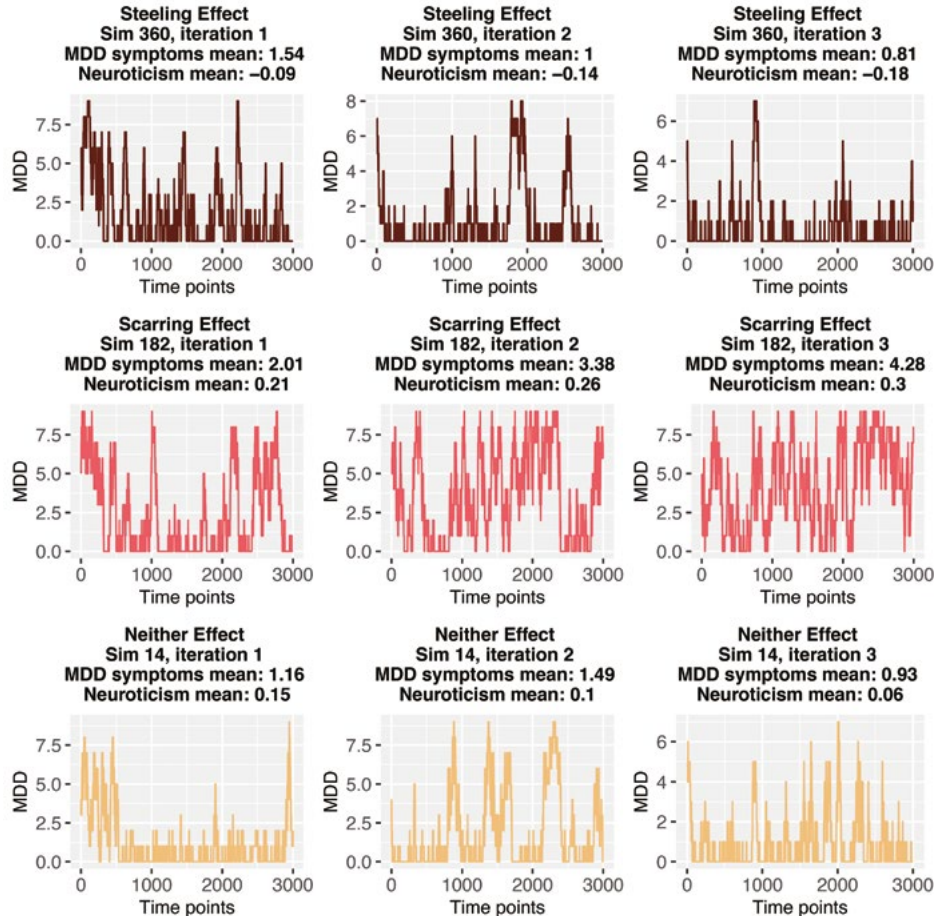


Figure 4.8: Individual simulated trajectories from the PRP model. The dynamics over time of three randomly selected sims from each group (scarring, steeling or neither effect) are plotted. The x-axis represents time, while the y-axis shows the sum score of the active MDD symptoms. The upper row shows the dynamics of a sim from the steeling effect group, the middle row the dynamics of a sim from the scarring effect group and the lower row the dynamics of a sim belonging to neither group. The expected values of MDD are calculated after 10.000 Glauber dynamics iterations, however, here we only show 3000 time points in order to increase the visibility of the dynamics.

4.4 DISCUSSION

In this chapter, we have proposed to model the relation between personality and psychopathology using interacting networks that operate on slow and fast time scales. At the level of the slow process, personality traits affect the threshold and connectivity parameters of the psychopathology symptom network, thereby affecting the resilience of mental health. At the level of the fast process, (alterations in) resilience of the psychopathology network can influence the slow process through scarring and steeling effects. This model is integrated, in the sense that it does not conceptualize personality and psychopathology as qualitatively and categorically distinct entities. In fact, in a nontrivial sense, the components of personality and psychopathology are the same: they both involve thoughts, affect states, and behaviors that influence each other. Items as characteristically worded in personality scales aim to pick up the average levels at which these components arise, while psychopathology symptoms tap distinct episodes of in- or decreases in these levels. Our model represents the way these processes interact, but should not be read as proposing an ontological distinction between the components themselves.

The implementation of a first order approximation to this theoretical model in a simulation, which connects empirically informed MDD and neuroticism networks, shows that the model results in plausible empirical patterns and can accommodate a) the strong correlation between MDD and neuroticism, b) the robustness of this correlation against removal of overlapping items, and c) individual differences in the effect of SLEs on depression and neuroticism. Thus, by taking a complexity perspective, we have been able to integrate personality and psychopathology into a single model with empirically plausible properties.

In the proposed model, the resilience of the psychopathology network influences the level of the traits in the personality network. In our simulation, we operationalize resilience by simulating the dynamics of the MDD network and comparing its equilibrium state with and without perturbations. The perturbations in this simulation are forcing all the nodes (symptoms) in the model to be active for one time point, which represents the situation of briefly being in a full-blown Major Depressive Episode after facing a stressful life event. In this way, we can study to what extent the system bounces back from these perturbations and compare the sum score of active symptoms for both situations with and without perturbations. Thus, in our simulation we alter the *state* of the nodes, which reflect activating the symptoms. Another interesting possibility for studying the resilience of networks would be to use percolation analysis, such as is done by Kennett and al. (2018). Here, the network *edges* are systematically removed until the point that the system collapses. The application of percolation methods to study the resilience of networks is a current topic of active research (van Borkulo et al., 2016). However, in the present study we are specifically interested

in how altering threshold parameters relates to symptom activation. Therefore, we have chosen to alter the symptom states, instead of the network edges. Even though the optimal operationalization of studying the resilience of psychological networks is beyond the scope of this chapter, we encourage future research to focus on this pressing issue.

The PRP framework is generic, meaning it does not only apply to specific disorders, personality traits or environmental factors, but provides a general way to study those specific contexts systematically. One can imagine extending the model in Figure 4.2 with other mental disorder symptoms on the borders of the PRP model. The exact influence of the different components of the model on each other, such as the environment on the fast symptom network, might vary across different types of mental disorders, personality factors, and life events. For example, a particular (childhood) trauma might have such a substantial, direct impact on mental health that the influence of personality on mental health plays a relatively small role (Isvoranu et al., 2016). Also, some mental disorders, such as depression, are highly heterogeneous, so that the disorder manifests itself in different combinations of symptoms for different people (Fried, 2017). Additionally, different symptoms may have distinct roles in the network, such as stabilizing the disorder state or communicating between various disorders (Blanken et al., 2018). Therefore, the impact of altering the thresholds of one mental disorder symptom will vary depending on the symptomatology of the individual and the network architecture. In this way, distinct symptom patterns can emerge from the architecture of psychopathology networks, with subtle differences in this architecture resulting in possibly large differences in vulnerability to disorders (Borsboom & Cramer, 2013, Borsboom, 2017). Instead of only focusing on mental disorders, the proposed PRP framework also offers a novel and fruitful way for investigating the relationship between personality and positive mental health, such as the positive impact of conscientiousness and agreeableness (Strickhouser, Zell & Krizan, 2017).

Although the simulation model built to implement the theoretical framework shows promising results, it is primarily intended to illustrate the operating principles of the PRP network. In many ways, the simulation model is a first approximation of the theory and as such it is subject to many limitations. For instance, the model is now solely informed by networks estimated on cross-sectional data, and although we suspect that such data will remain indispensable for assessing relations between symptoms, the simulation would ideally also be informed by longitudinal studies that chart the time dynamics of the system. How such data could be integrated into the model represents an important question for further research. Another interesting question for future research is how to specify the nature of the relationship between MDD and neuroticism. If one follows the reasoning in this chapter, future researchers could

focus on empirically validating the strong assumptions in our model regarding the supervenience relationship between personality and psychopathology.

Another limitation is that in the current setup the model can infinitely update the MDD symptom thresholds and neuroticism item scores. Undoubtedly, this is not a plausible empirical scenario. Not only should the MDD symptom thresholds and neuroticism items be updated within a certain interval, but updating should also consider that levels of personality may change for reasons other than the factors described here (i.e., independently of the steeling and scarring processes) as individuals age (Roberts, Walton & Viechtbauer, 2006). This also implies that the effect of psychopathology on personality, or vice versa, might be dependent on age. The PRP model may accommodate for this possibility by letting the scaling factors in the simulations be a function of time. Such work could also incorporate insights from studies investigating the underpinnings of slow changes in personality (Lodi-Smith & Roberts, 2007; Bleidorn, 2015; Bleidorn et al., 2013). Future research may thus focus on extending the PRP model in order to make it both more empirically plausible and suitable to represent differences between age groups.

The PRP network provides novel avenues for future research to explore therapeutic interventions for mental health. Since mental disorders are thought to emerge from direct symptom-symptom interactions (Borsboom & Cramer, 2013), it should, in theory, be possible to influence this development in an earlier stage, i.e., before the network has spiraled into a stable disorder state. The PRP network suggests that the resilience of mental disorders can be affected by personality dispositions, which in themselves are elements in an interconnected network. These direct interactions lay out various possibilities for psychotherapy, for example by intervening on the individual's tendency to worry frequently, thereby lowering the probability of developing the MDD symptom excessive worrying. Importantly, the PRP network offers a simple and transparent scenario for projecting the effects of such interventions in the slow process of personality on the psychopathology network.

The network perspective has successfully set out a novel research agenda that has led to many estimated network models from empirical data over a variety of psychological research fields (Robinaugh et al., 2020). The next question is how these estimated relationships between psychological variables arise, what causal processes they imply and how they develop over time. Therefore, theoretical work is needed to develop formal models that can inform specific hypotheses and thinking tools for studying these research questions (e.g., see: van der Maas et al., 2006; Cramer et al., 2016). In addition, if mental disorders really arise from a web of interconnected, clustering symptoms that evolve in an external field of life events and other factors (Fried et al., 2015; Borsboom, 2017), more research and theoretical work is needed on how to connect different sources of information as they relate to different features of this network.

The simulation work in this chapter can be regarded as a first attempt to achieve this, by integrating two different research fields, namely personality and psychopathology, into one dynamical model. In the past century, psychology has fruitfully isolated variables and studied them with standardized tests and methodologies, but now is the time to start connecting the dots again, and to build a theoretical framework that can generate the bigger picture of how all the parts of the human system work together to generate an integrated whole (Cervone, 2005).

5

INVESTIGATING DISTINCT EVOLUTIONS OF DEPRESSIVE COMPLAINTS USING COMPLEX DYNAMICAL NETWORKS

This chapter is under review for publication as:
Lunansky, G.*, Hoekstra, R. H. A.*, Blanken. T. F. (under review). Disentangling the role of affect in the evolution of depressive complaints using complex dynamical networks. https://psyarxiv.com/hv4cb/

**shared first authorship*

5.0 ABSTRACT

Many studies have found that depressive complaints are associated with the regulation of affect. Generally, studies either focus on the link between affect traits and depressive complaints in the population, or on short-term fluctuations in affect states and current depressive complaints within persons. In this chapter, we investigated how affect fluctuations relate to the evolution of depressive complaints both within and across people over longer periods of time. We included assessments of affect (Positive and Negative Affect Scale) and depressive complaints (Patient Health Questionnaire) in 228 participants who completed at least 20 assessments spanning between 9-14 weeks. We (i) explored affect trajectories, (ii) estimated longitudinal multilevel network models to examine the direct interplay between affect and depressive complaints, and (iii) investigated how individual network density relates to changes in depression severity over time. When separating affect trajectories based on depressive complaints, we identified that individuals consistently experiencing depressive complaints (PHQ > 4) report higher negative affect levels than positive affect. Contrary, individuals consistently reporting no depressive complaints (PHQ ≤ 4) showed the opposite pattern. Furthermore, the longitudinal networks included many and strong relations between the affects and depressive complaints. Lastly, we found a strong correlation between the density of individual networks and their change in depressive complaints. Thus, individual network density may indicate a more substantial aggravation or alleviation of depressive complaints. We conclude that affect fluctuations and change in depressive complaints are directly related, both within- and across individuals, and both within a single measurement moment and over time.

5.1 INTRODUCTION

Many studies have found that depressive complaints are associated with the regulation of affect (e.g., Gross, 1999; Joormann & Gotlib, 2010; Joormann & Stanton, 2016). Typically, affect is divided into positive affect (PA), for example, feeling inspired or enthusiastic, and negative affect (NA), such as feeling afraid or upset (Watson et al., 1988). PA is generally associated with a reduced risk of developing mood symptoms (Khazanov & Ruscio, 2016; Wichers et al., 2010), while NA is related to an increased risk of developing depressive symptoms (Wichers et al., 2007). This link between affect and depressive complaints has been investigated in the general population, showing how average levels of affect relate to average depressive complaints (e.g., Burke et al., 2018; Ripper et al., 2018) or within individuals, investigating how short-term fluctuations in affect states relate to current depressive complaints (e.g., Dejonckheere et al., 2019; Garnefski & Kraaij, 2006). As a result, these studies either focus on the link between affect traits and depressive complaints in the population, or on short-term fluctuations in affect states within persons.

However, both approaches have their limitations for interpreting the relation between affect and depressive complaints. Found associations from population studies (affects as traits) do not necessarily translate to the individual level (Hamaker, 2012; Molenaar, 2004). Alternatively, longitudinal studies (affects as states) mostly collect data within an intensive but brief timespan (e.g., five times a day for two weeks; Schoevers et al., 2021), capturing relations between momentary affect and current depressive complaints. As such, neither approach captures the relation between long-term affect fluctuations and the evolution of depressive complaints. In this study we aim to investigate how affect fluctuations and evolutions of depressive complaints are associated within and across people over longer periods of time (9-14 weeks, 11±1 (mean±SD)), during a prolonged period of stress as induced by the COVID-19 pandemic.

The current chapter uses data that are part of a longitudinal investigation from the Boston College, in which the repercussions of the COVID-19 pandemic on mental health were investigated (Cunningham et al., 2021). The studied period (March 20th 2020 until June 26th 2020) commenced a day after the first “stay-at-home” order was issued in California, which covers the moments leading up to the first large COVID-19 wave in the US. Clearly, this was a period of great uncertainty, and many effects on mental health problems during this time have been reported across all levels of society (Grolli et al., 2021; Kaufman et al., 2020; Pfefferbaum & North, 2020; Van Lancker & Parolin, 2020). We investigate how fluctuations in positive and negative affect relate to the evolution of mood complaints in the face of these perturbations. We study the affect trajectories of all individuals, and examine whether these trajectories differ for individuals with different depressive courses. In addition, we study which potential mechanisms may underlie the individual trajectories by estimating longitudinal

multilevel network models (Borsboom & Cramer, 2013; Epskamp, van Borkulo, et al., 2018; Epskamp, Waldorp, et al., 2018). These network models can estimate the direct interactions between affect and the depressive complaints for every individual and across individuals, within one measurement moment and across all measurement moments.

5.2 METHODS

The preregistration of this study can be found at the online repository of the Open Science Framework (https://osf.io/fw3np).

5.2.1 Participants

The data were obtained through the Boston College daily sleep and well-being survey (Cunningham et al., 2021). The study was set-up during the first wave of COVID-19 (March 20th 2020 until August 5th 2020) and participants were recruited online. All English-speaking individuals older than 18 were eligible to participate in the study, resulting in N=1,518 enrolled participants (mean±SD age 35.2±15.1 years old, range 18-90 years old). The participants provided informed consent, and the study received ethical approval from the Institutional Review Board at Boston College. More details on the study and recruitment can be found in Cunningham et al., 2021.

5.2.2 Procedure

The study started with a demographic survey, and upon completion participants received daily surveys on their sleep and well-being. The daily surveys were divided into a short and a full version, where the full version included additional questions containing validated assessments of mood (Positive and Negative Affect Schedule [PANAS]; Watson et al., 1988) and depression complaints (Patient Health Questionnaire-9 [PHQ-9]; Kroenke et al., 2001). The full version was sent on the first three days of the study enrollment. After enrollment, the long survey was sent on two randomly selected days of the week, and the short version was sent on the five remaining days. For a more detailed description on the assessments, we refer to Cunningham et al., 2021.

5.2.3 Materials

For the current study we include the demographics survey, PANAS items, and PHQ-9 assessments from the full version of the questionnaire.

5.2.3.1 PANAS

The PANAS is a 20-item questionnaire on the experience of positive (e.g., enthusiastic) and negative (e.g., scared) affects rated on a five-point Likert scale ranging from 1 ("very slightly/ not at all") to 5 ("extremely") (Watson et al., 1988). To reduce the number of variables for better power of the conducted statistical analyses (i.e., the

estimated network models described in section 5.2.5 Statistical analyses, we selected the ten items of the PANAS that have been validated in the short-form (Mackinnon et al., 1999). For the assessment of PA, these include: inspired, alert, excited, enthusiastic, determined, and for NA, these include: afraid, upset, nervous, scared, distressed. In the survey, participants were explicitly asked to rate how they felt in the *current moment* ("For each of the following attributes, indicate which description best describes how you currently feel, right now in the moment").

5.2.3.2 PHQ-9

The PHQ-9 is a 9-item questionnaire to measure depression severity by assessing each of the 9 DSM-IV criteria for depression on a four-point Likert scale ranging from 0 ("not at all") to 3 ("nearly every day") (Kroenke et al., 2001). In the current implementation, the item on suicidal thoughts was omitted. Participants were asked to rate the severity of complaints over the last *several days* ("In the last several days, how often have you been bothered by any of the following problems: not at all, some of the time, more than half of the time, almost all of the time").

5.2.4 Data selection and pre-processing

5.2.4.1 Study period

Since the full version of the questionnaire was sent out twice a week on random occasions, we selected the study period from March 20th 2020 until June 26th 2020, ending three days after the final full survey was sent out. Of the total number of participants enrolled in this study, N=1,355 (89.3%) completed at least one assessment between the selected study period.

5.2.4.2 Pre-processing of assessments

Sometimes participants completed the full survey multiple times on a single day: on 79 occasions, the survey was completed twice, and on two occasions the survey was completed three times. For these 81 assessments we chose the survey that was completed first. Inspecting the response rate of the full survey over the study period, a clear three-day interval pattern is seen (see the supplementary material, Figure 1-2). Therefore, we chose to group the days into 'measurement occasions', defined by a three-day window (e.g., March 20th-22nd 2020 is measurement occasion 1). In this way, the entire study period is grouped into 33 measurement occasions of three days each. The advantage of this grouping is twofold. First, it circumvents the problem of large differences in the number of completed surveys per assessment. Second, given that the full surveys were sent out randomly twice a week, dividing the assessments into three-day intervals makes the time between two completed surveys more equidistant. In case participants completed multiple surveys within one measurement occasion, we averaged their responses. Following the recommendations for estimating a multilevel model (Jordan, Winer & Salem, 2020), we selected participants who completed surveys

for at least twenty measurement occasions, resulting in a final sample size of N=228 participants (16.8%). Thus, for each included participant we have completed data for a minimum of 20 and a maximum of 33 measurement occasions that span 9-14 weeks, with an average of 11 weeks.

5.2.5 Statistical analyses

First, we inspect the affect trajectories for positive and negative affect over the studied time period during the COVID-19 pandemic. We plot the smoothed means of each affect over time using locally estimated scatterplot smoothing (i.e., a *loess* curve). Loess regression is a non-parametric method that fits least squares regressions in localized subsets of the data (Cleveland, 1979). The amount of smoothing that is applied depends on the number of data points that are used in each local regression (i.e., the neighborhood) and is controlled by setting the smoothing parameter α between 0 and 1. The larger the values for α, the more data points are being selected in the neighborhood (i.e., $n\alpha$ data points are selected, where n represents the total number of datapoints). More datapoints in the local regression results in smoother functions, that are more robust to fluctuations in the data. We set the smoothing parameter to α=0.2 in order to aid the visualization of patterns in the data, without losing sensitivity of fluctuations in the data.

Second, we aim to investigate whether potential differences in affect trajectories exist depending on the course of depressive complaints. To investigate this, we define subgroups based on clinically meaningful in- or decrease of depressive complaints, which we defined, in line with previous research, as a 5-point difference in their PHQ-9 total score (Lowe et al., 2004; Round et al., 2020). In addition, we will investigate whether we can differentiate between participants who consistently do not experience depressive complaints, defined as a PHQ-9 score of four or lower on all assessments; participants who experience occasional depressive complaints, defined as a PHQ-9 score higher than four on at least one assessment (and lower than four on at least one other assessment); and participants who experience consistent depressive complaints, defined as a PHQ-9 score consistently higher than four on all assessments (Kroenke et al., 2001).

Third, while these explorations will shed light on the relation between affect trajectories and depression course, they do not model the interactions among affect and depressive complaints directly. Therefore, we will more directly investigate their interplay by estimating a multi-level network model including both affect and depressive complaints. To estimate the relations while taking the longitudinal structure of the data into account we estimate a *two-step multi-level GVAR* model as implemented in the *mlVAR* package (Epskamp et al., 2017). Estimating a multi-level GVAR has two major benefits: (1) a single model can be estimated, leading to an adequately powered analysis, and (2) the within-person effects (reflecting *intra-*

individual differences) can be separated from between-person effects (reflecting *inter-*individual differences) (Epskamp, van Borkulo, et al., 2018).

The multi-level GVAR network model consists of *nodes*, which represent variables (in the current study: affect and depressive complaints), and *edges*, which represent the direct conditional associations between the nodes (Borsboom, 2017; Cramer et al., 2016; Epskamp, Borsboom, et al., 2018). The edges in the multi-level GVAR network are computed from partial correlations, meaning they portray the unique association among two variables after controlling for all other variables in the network. Edges can be positive or negative, indicating the corresponding nature of the associations between the nodes (Epskamp, Borsboom, et al., 2018).

The mlVAR package estimates three network structures: (a) a temporal network, (b) a contemporaneous network, and (c) a between-persons network (Epskamp, van Borkulo, et al., 2018). The temporal network indicates how well a variable predicts another variable at the next time point while controlling for all variables at the current time point. For example, a direct association from the depression complaint 'trouble concentrating' to the NA 'feeling distressed' indicates that having 'trouble concentrating' now predicts 'feeling distressed' at the next time point, taking into account all other current affects and depressive complaints. In the contemporaneous network we control for all these temporal effects, and show the unique association among variables within the same time window. For example, a direct and positive edge between 'feeling distressed' and 'feeling afraid' indicates that, within the same time window, these two negative affects are positively associated, after removing the lagged effects. Finally, the between-persons network shows the relationships among the means of persons in the data. For example, a positive edge between 'trouble concentrating' and 'feeling distressed' would indicate that persons who have, on average, more trouble concentrating also, on average, feel more distressed.

Fourth, based on the theorized role of affect dynamics in the course of depressive complaints, we expected the network structure to differ between people who experienced a meaningful change in their depressive complaints (either aggravation or alleviation) and people who did not experience such a meaningful change. Specifically, we expect that in more strongly connected networks, change in one affect or complaint can more easily "cascade" into other affects and complaints, thereby resulting in higher overall changes in depressive complaints over time. To explore this hypothesis we computed, for each participant, the average absolute strength of their temporal associations (i.e., their density; Oreel et al., 2019). Subsequently, we correlated their density to the maximum change in their PHQ-9 score over time: the difference between an individual's maximum PHQ-9 score, and their minimum PHQ-9 score over the course of 4 months. To compute this maximum difference, we take the order in which the scores occur into account, to capture whether an aggravation or

alleviation was experienced. For example, two individuals A (PHQ-9 scores: 3,7,6,8,6) and B (7,8,4,4,3) who both have a minimum PHQ-9 score of 3 and a maximum PHQ-9 score of 8, but differ in their PHQ-9 difference score reflecting their aggravation (A: maximum difference 3-8=-5) or alleviation (B: maximum difference 8-3=5). The PHQ-9 difference score indicates the maximum change in depressive complaints this individual reported over the study period.

All analyses were performed in R (version 4.0.5) using the packages *'ggplot2'*, *'mlVAR'*, *'qgraph'*, *'dplyr'*, *'nnet'*, and *'ggpubr'*. The derived data used for analyses and corresponding code can be found on the Open Science Framework (OSF): https://osf.io/2zh4f/.

5.3 RESULTS

5.3.1 Sample characterization

We included 228 participants that completed assessments on at least 20 measurement occasions within March 20th 2020 and June 26th 2020. Over the course of four months, on average, participants completed 23±3 (mean±SD) assessments. The majority of the participants were female (n =186, 81.58%) and, on average, 45±19 (mean±SD) years old. Two-hundredth-seven participants identified as white (90.8%). Most participants lived in a western country (n=221, 96.9%), from which most lived in the United States (n=198, 86.8%). The median reported annual income was between 50,001 - 75,000 USD. Half of the participants had a graduate, medical or professional degree (n=116, 50.9%). For more details on sample characterization see the supplementary materials of this chapter.

First, Figure 5.1(a) shows the affect trajectories across the 33 measurement occasions for all participants concertedly. Averaging over all participants shows that PA is generally rated somewhat higher than NA, and that this is consistent over the entire study period.

Second, we inspected the affect trajectories for different groups based on (i) their change in depressive complaints over time, and (ii) the severity of the experienced depressive complaints. Over the studied time period, 116 participants experienced a meaningful change in their depression symptomatology: 56/116 participants (48.3%) experienced an aggravation in their depressive complaints (i.e., an increase in PHQ-9 score of at least 5), and for 60/116 participants (51.7%) their depressive complaints alleviated (i.e., a decrease in PHQ-9 score of at least 5). Splitting the affect trajectories for each of these groups, shown in Figure 5.1(b), indicates that in both groups, on average, the affects are more intertwined. Interestingly, no marked differences are seen in participants who experienced an aggravation of their complaints compared with participants who experienced an alleviation of their complaints.

Grouping participants into the consistency of their depressive complaints, we found that 50/228 participants (21.9%) were consistently without depressive complaints,

137/228 participants (60.1%) experienced depressive complaints at least occasionally, and 41/228 participants (18.0%) experienced depressive complaints consistently. Figure 5.1(c) shows the affect trajectories for each of these groups. Here, we see clear differences in affect trajectories across the three groups: in people without depressive complaints there is, on average, a clear distinction between the PA scores, which are rated relatively high, and the NA scores, which are all rated consistently low. In the people with occasional depressive complaints, the PA scores are, on average, still rated higher than the NA scores, but the distinction is less clear. Finally, in people who consistently experience depressive complaints, the ratings of positive and NA have flipped, as NA is, on average, rated higher than PA.

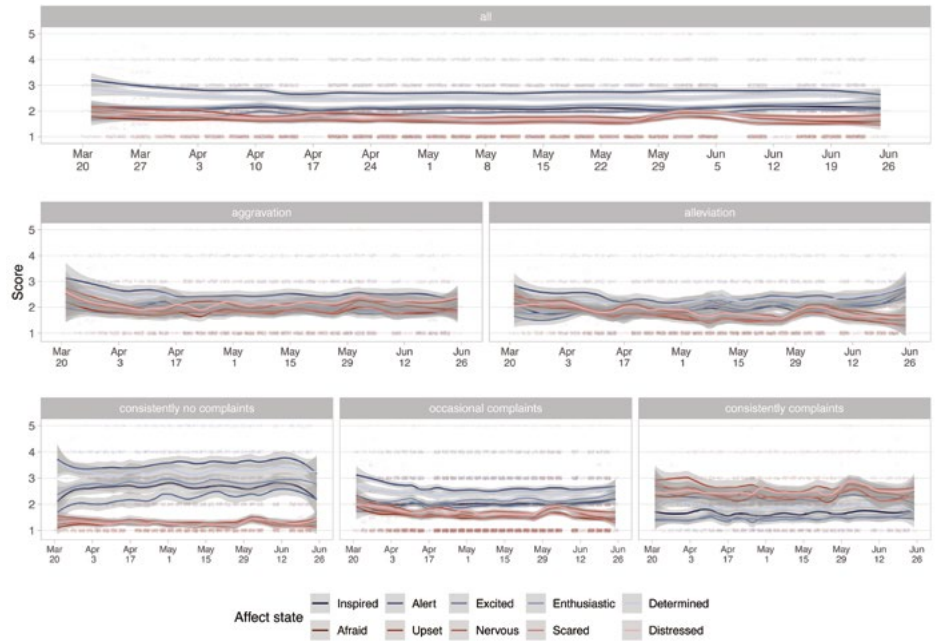


Figure 5.1. Affect trajectories from March 20th 2020 (measurement occasion 1) until June 26th 2020 (measurement occasion 33). Panel (a) shows the smoothed conditional mean trajectories of all participants for each of the affect states, together with its 95% confidence interval (shaded area). Panel (b) on the left shows the trajectories for participants whose depressive complaints aggravated during the study period, and on right shows the trajectories for participants whose depressive complaints alleviated during the study period. The (c) panels show the trajectories for participants who consistently experienced no depressive complaints (left), those that occasionally experienced at least mild depressive complaints (middle), and those that consistently experienced depressive complaints (right). Blue lines correspond to the smoothed conditional means of the positive affect states 'inspired', 'alert', 'excited', 'enthusiastic', and 'determined'; and red lines correspond to the smoothed conditional means of the negative affect states 'afraid', 'upset', 'nervous', 'scared', and 'distressed'. Affect states are scored on a Likert scale from 1 to 5. Decimal scores were obtained when participants completed multiple assessments within one measurement occasion.

Third, we investigated the dynamical relations among affect and depressive complaints by estimating a multilevel network model. Figure 5.2 shows the three estimated network structures: (a) the temporal associations averaged over all participants; (b) the contemporaneous associations averaged over all participants; and (c) the between-persons network structure. The temporal network shows many associations between affect and depressive complaints, indicating a direct interplay between affect and depression. Compared with the temporal network, the contemporaneous network shows clearer demarcations between PA, NA and depressive complaints: there are comparatively stronger edges within than between the three domains. This might indicate that within one measurement occasion the experience of PA, NA, and depressive complaints is relatively independent. The between-persons network portrays more relations between the different domains compared with the contemporaneous network, indicating that the average affect people experience is related to their average depressive complaints.

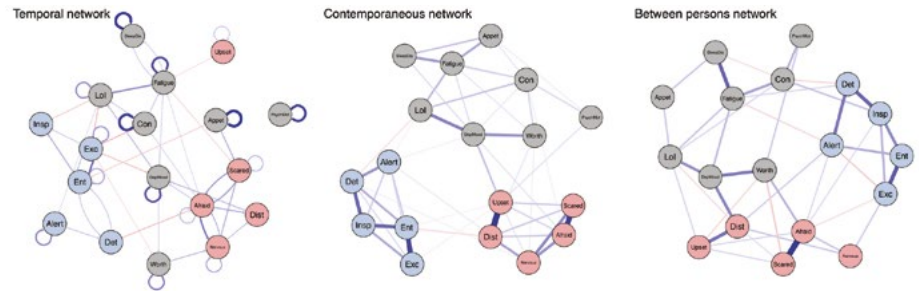


Figure 5.2. Output from mlVAR for n=228 and t> 20. Left, the temporal network model is displayed, portraying the average within-person relations from one measurement occasion onto the next. The center displays the contemporaneous network model, portraying the average within-person effects in the same measurement occasion, after controlling for the temporal effects. Right, the between-persons network model is displayed, indicating the average effects between persons. Blue edges indicate positive relations, whereas red edges indicate negative relations. Node colors correspond to PA (light blue), NA (salmon pink), and depression complains (grey). Abbreviations: Insp = inspired; Alt = alert; Exc = excited; Ent = enthusiastic; Det = determined; Afr = afraid; Ups = upset; Ner = nervous; Scar = scared; Dist = distressed; LoI = loss of interest; DepMood = depressed mood; SleepDis = sleep disturbances; Appet = loss of appetite; Worth = feelings of worthlessness; Con = concentration problems; PsychMot = psychomotor agitation or retardation.

Interestingly, the separation between the different network components (i.e., PA, NA, and depressive complaints) seems less evident in the temporal network compared to the contemporaneous and between-persons network; there are relatively more edges between components vs. within components within the temporal network. Post-hoc clustering analyses confirmed the original three components in the contemporaneous network and the between-person network; however, these components were not confirmed for the temporal network (see the supplementary materials, Figure 3-4).

Depending on the clustering algorithm (spinglass or walktrap), 4 to 5 clusters were found within the average temporal network. These clusters were a mix of different affects and depressive complaints (see the supplementary materials).

Lastly, to further investigate the relations between affects and depressive complaints, we correlated individuals' network density of the temporal network to their maximum change in PHQ-9 score. As shown from the correlation plot in Figure 5.3 (right panel), there is a strong correlation (r = 0.77) between individual network density and maximum absolute change in PHQ-9 score. Stronger network densities relate to both a more substantial aggravation and to a more substantial alleviation in their depressive complaints, as can be seen from the bifurcation in Figure 5.3 (left panel) illustrating the correlation between individual network density and change in PHQ-9 score.

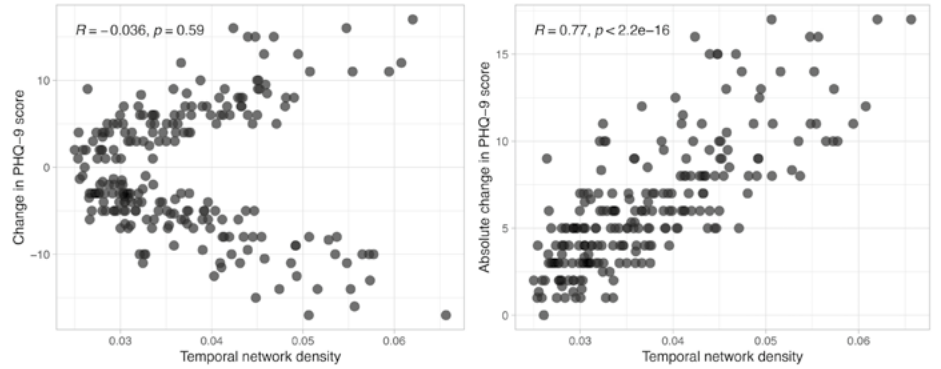


Figure 5.3. Individual network density and change in depressive complaints. In the left panel the correlation between individual network density and maximum change in PHQ-9 score is shown. In the right panel the correlation between individual network density and the absolute maximum change in PHQ-9 score is shown.

5.4 DISCUSSION

In the current chapter we set-out to investigate the dynamic interplay between affect and depressive complaints during a prolonged and eventful time imposed by the COVID-19 pandemic. The unprecedented dataset allowed us to investigate how affect fluctuated over time, for different levels of depression severity and consistency. At first sight, affect fluctuations seem relatively stable over time, in which, on average, participants reported somewhat higher levels of PA than NA. However, we found different results when separating the affect trajectories based on the participant's depressive complaints. Interestingly, while the affect trajectories were similar for people experiencing either an aggravation or alleviation of depressive complaints, we found marked differences in the trajectories among people who experienced consistently no depressive complaints compared with consistent depressive complaints. Specifically,

the experienced affect seemed to 'flip' depending on the severity of one's depressive complaints. Crucially, these differences pertained to both PA and NA trajectories, showing that there is a clear link between depressive complaints and both positive and negative affect.

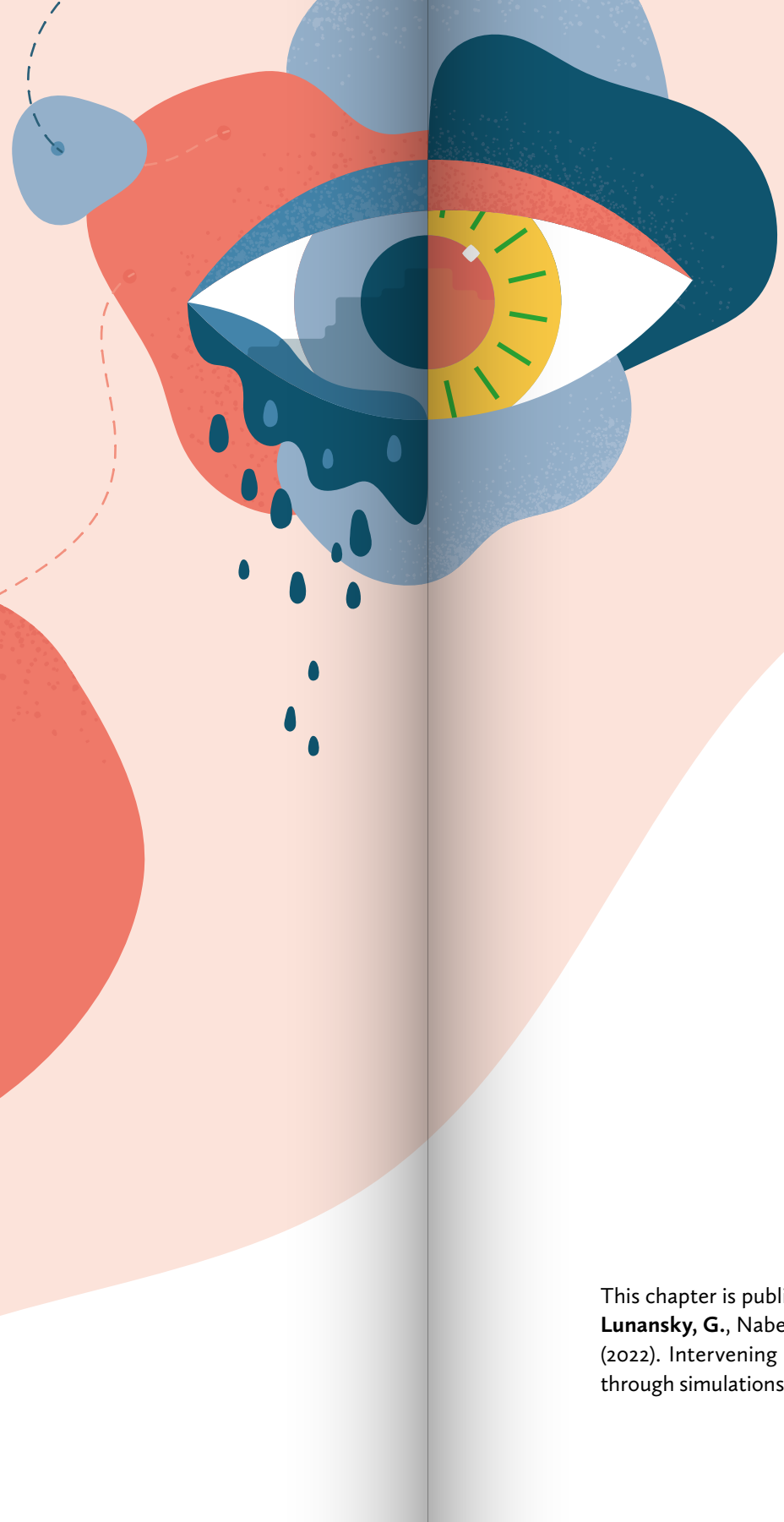
We subsequently investigated the link between affect and depression more directly, and network models revealed many and strong relations between the affect and depressive complaints, showing that both are indeed directly linked, both within- and across persons, and both within a single time point and over time. We identified three clear clusters of variables - pertaining to PA, NA and depressive complaints - in the contemporaneous and between-subject networks. Interestingly however, we did not find these clusters in the temporal network. This suggests that the relations among affect and depressive complaints within persons over time may be substantially different from their relations within one timepoint or between-persons.

Furthermore, we found a strong relation between the strength of the links in an individual's temporal network (i.e., the density) and the absolute change in PHQ-9 score. Interestingly, when considering the direction of change – alleviation or aggravation in PHQ-9 score – a bifurcation appeared, indicating that the same network density can relate to either a worsening or improvement in depression complaints. Crucially, this finding reflects a well-known property of test reliability, namely that the variance of a total score (in our case the change in depression complaints) consists of the sum over the variance in all items (in our case the individual affects and individual PHQ-9 items) and the sum over their covariances (Cronbach, 1951). Clearly, denser networks indicate stronger covariances, that is necessarily reflected in the variation of the sum score (i.e., the variation in PHQ-9 score). While this is a statistical necessity, this is, to the best of our knowledge, the first time that it has been shown in relation to individual psychopathology networks. This has important implications for the clinical interpretation of networks, as network density has generally been related with more severe psychopathology (e.g., see Calugi et al., 2021; Cramer et al., 2016; van Borkulo et al., 2015). However, our study shows an alternative situation in which a larger density of individual networks indicates more fluctuations and potential for flexibility (Hayes et al., 2015).

Some limitations warrant attention. First, the questionnaires were sent out twice a week at random intervals, thereby violating the assumption of equidistant measures for longitudinal analyses. We circumvented this problem in part by defining measurement occasions as three-day periods. Second, it should be noted that while we are interested in mechanisms of change, the current available network estimation techniques assume that the mean and variance of the time series data remains the same (i.e., stationarity) (Jordan et al., 2020). However, alternative time-varying network models require many more datapoints than present in the current dataset (e.g., see Haslbeck et al., 2020).

Therefore, there is a mismatch between our data, our interest in change, and the available statistical models.

To conclude, we found that fluctuations of affect are directly related to the course of depressive complaints, both within- and across individuals, and both within a single measurement moment and over time. At first sight, affect trajectories over time seemed stable, even in the eventful time of COVID-19. However, marked differences in the affect trajectories appeared when separating individuals based on the consistency and severity of their depressive complaints. The conducted network analyses showed that there are direct interactions between affect, for both PA and NA, and depression complaints. The direct links between these domains was found when averaging over all individuals, and both within one measurement moment as over time. On the individual level, we showed that the stronger affect and depressive complaints are overall connected over time, the larger the change is in depressive complaints. Together, these findings shed light on the potential underlying mechanisms of change and development of mental disorders.



6

INTERVENING ON PSYCHOPATHOLOGY NETWORKS THROUGH SIMULATIONS

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6.0 ABSTRACT

Identifying the different influences of symptoms in dynamic psychopathology models may hold promise for increasing treatment efficacy in clinical applications. Dynamic psychopathology models study the behavioral patterns of symptom networks, where symptoms mutually enforce each other. Interventions could be tailored to specific symptoms that are most effective at lowering symptom activity or that hinder the further development of psychopathology. Simulating interventions in psychopathology network models fits in a novel tradition where symptom-specific perturbations are used as *in silico* interventions. Here, we present the *NodeIdentifyR* algorithm (NIRA) to identify the projected most efficient, symptom-specific intervention target in a network model (i.e., the Ising model). We implemented NIRA in a freely available R package. The technique studies the projected effects of symptom-specific interventions by simulating data while symptom parameters (i.e., thresholds) are systematically altered. The projected effect of these interventions is defined in terms of the expected change in overall symptom activity across simulations. With this algorithm, it is possible to study (1) whether symptoms differ in their projected influence on the behavior of the symptom network and, if so, (2) which symptom has the largest projected effect in lowering or increasing overall symptom activation. As an illustration, we apply the algorithm to an empirical dataset containing Post-Traumatic Stress Disorder symptom assessments of participants who experienced the Wenchuan earthquake in 2008. The most important limitations of the method are discussed, as well as recommendations for future research, such as shifting towards modeling individual processes to validate these types of simulation-based intervention methods.

6.1 INTRODUCTION

Recent research focuses on the distinct roles that symptoms may play in the development of psychopathology (Blanken et al., 2018). For example, some symptoms could have stabilizing effects, meaning that once they are present, they also activate related symptoms (e.g., the presence of the depressive symptom "fatigue" also leads to the activation of the symptom "loss of energy"; Borsboom & Cramer, 2013). In this way, these stabilizing symptoms may influence the spread of symptom activity and the development of psychiatric disorders. Investigating whether symptoms have different roles in the onset and development of psychopathology and, if so, developing a methodology to identify the most influential symptoms could have promising clinical implications for increasing treatment efficacy (Boschloo et al., 2019; Chekroud et al., 2017). Clinical interventions could be tailored to specific symptoms that are most effective in lowering symptom activity or that hinder the further development of psychopathology.

Treatments for mental disorders already make use of symptom-specific interventions. For example, in the case of Generalized Anxiety Disorder (GAD), interventions exist for a distinct type of worrying problems using Cognitive Behavioral Therapy (CBT; Dugas & Ladouceur, 2000). In the case of Major Depressive Disorder (MDD), specific treatment programs have been developed for suicidal behavior (DeCou et al., 2019). Symptom-specific interventions are also being developed in clinical trials, such as particular CBT for psychosis which focuses on treating hallucinations or delusions (Lincoln & Peters, 2019). Furthermore, symptom-specific treatments are used in experimental settings, such as randomized controlled trials, to compare the specific effects of different treatment conditions, for example, between psychotherapy and psychopharmacology (Bekhuis et al., 2018). By using novel technology, "micro-interventions" can be administered via smartphones as a personalized approach to target the depressed mood symptom (Meinlschmidt et al., 2016). However, it is vital to consider the propelling effects from intervening on one symptom to other symptoms due to their potential interrelatedness (Boschloo et al., 2019).

An established framework to study psychopathology as an interrelated, dynamic system of symptoms is the network theory of mental disorders (Borsboom, 2017; Borsboom & Cramer, 2013; see Figure 6.1). The network theory of psychopathology has been applied to a variety of psychiatric disorders (e.g., for MDD, see Cramer et al., 2016; for GAD, see Beard et al., 2016; for Post-Traumatic Stress Disorder, see Armour et al., 2017; for Psychosis, see Isvoranu et al., 2017; and for Autism Spectrum Disorder, see Deserno et al., 2017). According to this theory, symptoms are not passive manifestations of one underlying mental disorder that acts as the common cause. Instead, symptoms play an active part in developing and maintaining psychopathology. By representing psychopathology as a dynamic system, symptoms are no longer

(statistically) exchangeable, meaning they could play different roles in the maintenance and development of psychiatric disorders (Blanken et al., 2018; Borsboom, 2017).

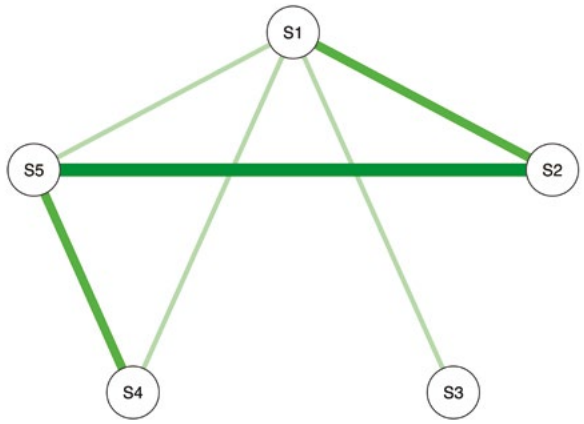

Figure 6.1. An example of a symptom network model. A hypothetical symptom network model for five psychopathology symptoms (S1-S5). Circles in the network represent nodes, which refer to the symptom variables (S1-S5). Lines that connect the circles represent edges, where green (red) lines represent positive (negative) associations. The thickness of the edges represents the magnitude of their association. In this hypothetical network, there is a relatively strong association between S5 and S2, which means that if S2 is activated, S5 is likely to activate as well, and vice versa. Contrary, there is no direct relation between S3 and S4 when controlling for the other nodes in the network (S1, S2, and S5).

Various statistical network models have been developed over the past years that analyze the co-occurrence of symptoms estimated from data, using, for example, clinical interviews or questionnaires (e.g., see Epskamp et al., 2018; Haslbeck & Waldorp, 2020; van Borkulo et al., 2014). In these network models, *nodes* represent symptoms, and *edges* represent the unique associations between symptoms (see Figure 6.1; Borsboom & Cramer, 2013; Epskamp, Waldorp, et al., 2018). Edge parameters are called edge weight parameter, and denote the unique, weighted (i.e., edges can be present with a certain strength), statistical associations between a pair of symptoms when controlling for the presence of all other symptoms in the network (Epskamp, Borsboom, et al., 2018). Positive (negative) edge weight parameters denote positive (negative) associations. For example, suppose two symptoms such as "worry" and "irritability" are strongly positively associated. In that case, the theory proposes the hypothesis that the presence of the "worry" symptom leads to the activation of the "irritability" symptom as well, and vice versa (Borsboom, 2017; Borsboom & Cramer, 2013). Different methods are used to estimate the edge weights, depending on the model used and the scale of the raw data. For example, in network models estimated from continuous data, such as the Gaussian Graphical Model (GGM; Epskamp, Waldorp, et al., 2018), edge weights are computed from the partial correlations of each

pair of nodes. To obtain sparsity and account for false-positive edges, regularization is imposed on the network structure, meaning that small edge parameters are shrunk to zero (the most-used regularization technique is *lasso,* see van Borkulo, et al., 2014, and Epskamp & Fried, 2018, for details). Furthermore, network models can also have parameters for the disposition of symptoms to manifest, which can be strong or weak (e.g., see Haslbeck et al., 2020; Marsman et al., 2017; Marsman et al., 2018; van Borkulo et al., 2014). A symptom with a strong disposition to be "off", for example, 'suicidal ideation', requires much 'input' such as stress before it will manifest.

To assess the relative importance of symptoms in psychopathology networks estimated from observational data, the concept of *node centrality* was received with high hopes (Spiller et al., 2020). Centrality indices stem from the domain of social networks, in which the most central node in the network has the largest number of edges with neighboring nodes and the most substantial edges (Newman, 2010). The concept was translated to psychology (Cramer et al., 2010), where the *centrality hypothesis* states that the most central nodes are the best intervention targets, as they are thought to represent the most influential nodes in a network (Robinaugh et al., 2020). Therefore, centrality metrics are used in psychopathology networks to identify possible intervention targets (Borsboom & Cramer, 2013; Epskamp, Borsboom, et al., 2018; Fried et al., 2018; Spiller et al., 2020; Stochl et al., 2018). However, several researchers have raised doubts regarding the suitability of centrality indices in psychological networks (Bringmann et al., 2019; Castro et al., 2019; Dablander & Hinne, 2019; Hallquist et al., 2019; Rodebaugh et al., 2018; Spiller et al., 2020). Centrality indices are based on the *structure* of the psychological network (i.e., the presence and strength of edges), but do not explicitly consider the *dynamics* of the network (i.e., how symptoms influence each other's presence). It is not evident how the structure of statistical network models relates to causal influences of symptoms: a causal process running over the network structure needs to be assumed before one can assess causal claims (Dablander & Hinne, 2019; Haslbeck, Ryan, et al., 2021; Henry et al., 2021).

A developing novel tradition studies the projected influences of symptoms in psychopathology models using simulated symptom-specific perturbations as *in silico* interventions (Burger et al., 2020; Castro et al., 2019; Henry et al., 2021; Robinaugh et al., 2016). By altering characteristics of the symptom network, such as systematically deactivating symptoms (i.e., altering the symptom variables' *state*) the symptom's projected influence on the behavior of the network can be studied (see for example: Castro et al., 2019; Henry et al., 2021; Robinaugh et al., 2016). For example, the value of a symptom such as "loss of energy" is set to zero to simulate its treatment effect on the rest of the network. The procedure is repeated for all other symptoms in the network. The projected impact of this symptom-specific intervention is calculated as the change in the overall symptom sum score. The node with the most significant

expected influence is the node that propels the most substantial change in the next simulation iteration (Robinaugh et al., 2016).

However, the clinical representation of simulating an intervention by altering the symptom's state (i.e., forcing the symptom to be absent) does not take into account that nodes all have different dispositions for manifestation. The different dispositions of symptoms make interventions differ in their effectiveness to treat symptoms (Barth et al., 2016). Furthermore, from a clinical perspective, it is unlikely that a treatment intervention will forever push the presence of a symptom to zero. Instead, interventions are more likely to lower the *probability* of symptoms being present. In other words, symptoms may still be present from time to time, but after the intervention, they are less likely to occur. Therefore, a better clinical representation of simulating interventions would be the alteration of symptom *parameters* in a network model.

Symptom parameters can be altered in two ways: by increasing or decreasing the nodes' internal dispositions for activation. A symptom's disposition for activation can be decreased so that it is less likely to manifest. This would mimic a clinical intervention on a specific symptom, which we call an *alleviating intervention*. When done systematically, one can study which alleviating intervention on a specific symptom in a network model has the most substantial projected effect on lowering overall symptom activity. Contrary, a symptom's parameter can also be increased such that it is *more* prone to activation, which we call an *aggravating intervention*. This would mimic the effect of a stressful event on the symptom, increasing its probability of manifestation. Aggravating interventions are used to study which symptom would have the most substantial projected effect on deteriorating the network's state in a stressful event.

This chapter presents an algorithm that outlines node-specific target points for interventions on psychopathology networks, which are estimated from observational data. The algorithm focuses on the clinical importance of a symptom by altering its parameter and studying its projected effect on the behavior of the network. With this algorithm, it is possible to study (1) whether symptoms have distinct projected influences on the behavior of the network, and if so, (2) which symptom has the most substantial projected effect after an alleviating intervention and aggravating intervention. In the following section, the algorithm is explained and applied to an empirical dataset containing assessments of Post-Traumatic Stress Disorder (PTSD) symptoms.

6.2 METHODS

In this section, we explain the rationale behind the proposed technique. Furthermore, we outline the analysis design to apply the technique to an empirical dataset of PTSD symptoms.

6.2.1 NodeIdentifyR algorithm

We present the *NodeIdentifyR* algorithm (NIRA) to identify the projected most efficient, symptom-specific intervention target in psychological networks[8]. This technique studies the projected effects of symptom-specific interventions by simulating data when symptom parameters are systematically altered. The effect of these perturbations is calculated as the change in overall symptom activation of the network.

6.2.1.1 Model

The algorithm uses the Ising Model as a representation of psychopathological dynamic systems. The Ising model originates in physics and describes the interaction between states of particles connected in a network (originally, the Ising model was constructed to explain magnetism; Ising, 1925). Since the model's characteristics align with the network theory of psychopathology, it is often used as a statistical model of symptom networks (Marsman et al., 2018; van Borkulo et al., 2014). The model is sufficiently simple to be mathematically tractable and, at the same time, sufficiently rich to represent important phenomena of mental disorders. For example, the presence of alternative stable states (i.e., the system can be in a healthy state or disorder state), critical transitions (i.e., the system can suddenly jump towards a disordered state when faced with enough stress), and hysteresis (i.e., once the system is stuck in the disordered state, it requires a stronger reduction of stress to recover than the original level of stress that caused the critical transition; Cramer et al., 2016). The Ising model uses binary data, meaning that symptoms can be "on" or "off".

The Ising model is estimated using logistic regression analyses. Edge weights are the coefficients from logistic regression analyses, in which symptom variables are iteratively regressed on all other symptoms except the symptom variable itself (Marsman et al., 2018; van Borkulo et al., 2014). The intercept of the logistic regression represents the *threshold parameter* of every symptom, which denotes the symptom's disposition for manifestation (Marsman et al., 2018; van Borkulo et al., 2014). Positive (negative) thresholds denote the symptom's disposition to be activated (deactivated) if all other

8 The *nodeIdentifyR* R-package can be downloaded via: https://github.com/JasperNaberman/nodeIdentifyR

symptoms are absent[9] (Dalege et al., 2018). Threshold parameters differ over symptoms and are weighted, in which a higher magnitude indicates a larger probability that the symptom will be (de)activated. See the supplementary materials for the formula of the Ising model's dynamics.

6.2.1.2 Interventions

All analyses and simulations are executed using the statistical software program *R*. NIRA runs multiple simulations, in which interventions are administered by systematically altering the threshold parameters of the estimated network model. One simulation will be executed with all the original threshold parameter values, and afterward, one simulation will be done for every symptom-specific intervention. To be precise, NIRA will generate 5000 observations or simulated 'participants' for which symptoms are assessed after interventions. For example, to study the effect of one intervention in a network containing ten symptoms, 11 x 5000 observations will be generated: once with all original threshold parameter values and ten times for every iteratively changed threshold parameter. Response simulations are computed with the R package *IsingSampler* (Epskamp, 2020), which samples states from the probability distribution of the Ising model. NIRA uses the Metropolis-Hastings algorithm implemented in *IsingSampler* for data generation to ensure the process will remain computationally feasible in a multivariate distribution (Epskamp, 2020). Note that the Metropolis-Hastings algorithm does not return the exact likelihood but a pseudo-likelihood; the exact likelihood can be computed for small networks (up to ~ ten nodes) with the function *IsingLikelihood*, but this is infeasible for larger networks due to the intractability of the Ising model (Epskamp, 2020).

Two types of interventions can be administered. Alleviating interventions decrease a symptom's threshold by subtracting some value from its original threshold parameter, and aggravating interventions increase its threshold by adding some value to its original parameter. The magnitude of the intervention, specifically, the value with which the threshold parameters are increased or decreased, determines the strength of the intervention on the network's behavior (i.e., the intervention's effect size). Many different possibilities exist to determine a rule of how thresholds should be altered. We choose to use the standard deviations of the estimated thresholds: After estimating the model, we store the threshold of every symptom in a vector and compute its standard deviation. The standard deviation will be used to alter (i.e., add to or subtract from) the symptoms' estimated threshold parameters one by one. In the current study, NIRA alters the estimated value of the threshold parameter in question with two times that standard deviation. In this way, the magnitude of the intervention

9 Depending on the specific model used, and the possible values of the nodes, the threshold parameter could also take a value between 0 and 1, where 0.5 indicates no preference, 0 indicates a preference for deactivation and 1 indicates a preference for activation. See Haslbeck et al., 2020 for an extensive discussion.

is somewhat bound to the estimated thresholds of all symptoms in the network. A potential downside is that the magnitude of the intervention depends on the raw data and changes over different datasets. However, choosing a fixed magnitude (e.g., subtracting or adding a value of one to the thresholds) is suboptimal since its effect size will also change depending on the original value of the estimated threshold parameters (i.e., since the model is non-linear, changing a threshold from -3 to -2 has a different effect than changing the threshold from -1 to 0). In the R-package, the magnitude of the intervention can be adjusted to the number of standard deviations of choice. See the supplementary materials for a sensitivity analysis with interventions that alter the threshold parameters with one instead of two standard deviations.

Furthermore, it is important to note that when simulations are used to study projected effects, the simulated behavior of the model needs to converge to a stable state to ensure results are robust (see, e.g., Danvers et al., 2020). Multiple iterations are necessary to ensure that the simulated behavior is robust and replicable (Nilmeier et al., 2011). Therefore, we will simulate the effect of interventions on the behavior of the symptom networks until the model has converged to a stable state (See the supplementary materials for stability analyses of NIRA using various numbers of iterations).

6.2.1.3 Determining the most effective target

To study the projected effect of an intervention on the entire network, sum scores are inspected. The sum score of a simulated observation equals the sum of all data points for that observation. Since the Ising model uses binary data, responses are decoded as either 0 or 1, indicating the symptom's absence or presence. In an exemplary questionnaire consisting of ten items, the sum score of each observation can range from zero to ten. Higher scores indicate higher levels of psychopathology. The use of sum score analyses in a simulation environment to measure the impact of specific perturbations can be used effectively to measure the overall state of a dynamic system (Dalege et al., 2017). The NIRA outcome will be computed as the absolute difference between the baseline network's sum score (without interventions) and the sum scores after every threshold alteration for alleviating and aggravating interventions. The node-specific intervention with the highest absolute difference is the node with the strongest projected effect on the network's behavior.

6.2.2 An empirical application to PTSD

As an empirical illustration, NIRA is applied to a dataset containing PTSD symptoms. Three research questions are investigated: (1) Do symptoms differ in their projected influences on the network's behavior after symptom-specific interventions? (2) Are identical symptoms identified by NIRA for alleviating interventions and aggravating interventions? (3) Is the most efficient target symptom identified by NIRA also the most central symptom?

6.2.2.1 Data

The empirical dataset contains PTSD symptom assessments gathered after the 2008 Wenchuan earthquake. The sample consisted of 4910 adolescents (49.5% boys; mean age 11.4±1.4 years) who experienced the earthquake and was measured 2.5 years after the earthquake. Their 17 DSM-IV PTSD symptoms were assessed by the 17 items in the Chinese version of the University of California, Los Angeles PTSD Reaction Index questionnaire (PTSD-RI; Steinberg et al., 2004), a validated self-rated 5-point Likert scale (from 0 = never to 4 = most of the time). Missing item-level values were estimated using maximum likelihood (ML) procedures as suggested by (Schafer & Graham, 2002). To estimate the Ising models, we binarized the symptom scores into 0 (original score was 0) and 1 (original score ranged from 1 to 4), respectively, representing symptom absence and (at least some level of) symptom presence.

6.2.2.2 Design

NIRA uses the *IsingFit* R package (van Borkulo et al., 2014) to estimate the Ising Models and the *qgraph* R package (Epskamp et al., 2012) to visualize the networks. NIRA is applied twice to the network: once with alleviating interventions and once with aggravating interventions. To study the relationship between the size of the original threshold values and the ordering of the projected most effective intervention targets, the correlation between the novel threshold values after interventions and the NIRA outcome will be computed.

6.2.2.3 Comparison with strength centrality

Node centrality indices, precisely *strength centrality,* are calculated using the *qgraph* R package (Epskamp et al., 2012). Strength centrality is defined as the sum of the absolute weighted edge strengths, where the sum is taken over edges connected to the relevant node (Cramer et al., 2010). Nodes with higher strength centrality have more and stronger connections with neighboring nodes and are therefore often hypothesized to be more influential in the spread of symptom activity (Rodebaugh et al., 2018). Stability studies have shown that strength centrality is the most robust centrality measure of all used centrality indices in psychological networks, especially in ordering symptoms (Epskamp, Borsboom, et al., 2018). We will therefore compute the correlation between strength centrality and NIRA.

6.3 RESULTS

Figure 6.2 shows the estimated Ising model network from the PTSD symptoms. Nodes in the networks represent 17 PTSD symptoms from three subdomains: Intrusion, Avoidance, and Arousal (see Table 6.1).

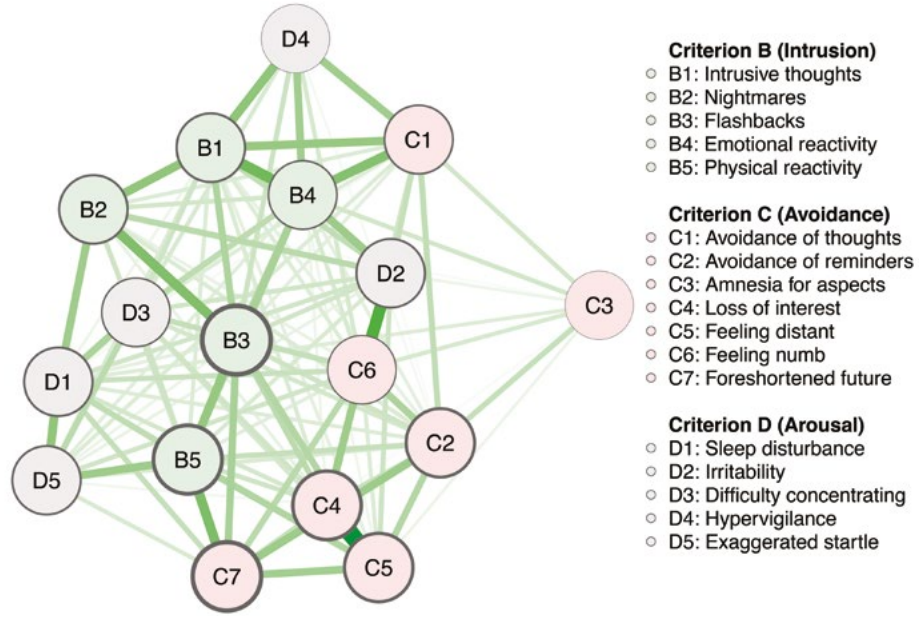

Figure 6.2. Estimated Ising network model for 17 PTSD Symptoms in the Wenchuan earthquake study (N=4910). Nodes in the networks represent the 17 PTSD symptoms. Symptoms are grouped by color based on their clinical subdomain (Intrusion, Avoidance, and Arousal). The thickness of node borders represents the absolute value of the nodes' threshold parameters. All symptom thresholds indicate a disposition towards being absent (i.e., they have a negative threshold value), except the threshold of node "D1" which has a weak disposition towards being present (i.e., the symptom has a weakly positive threshold).

6.3.1 Interventions

First, NIRA was applied to the Ising model using alleviating interventions (see Figure 6.3; panel A). Results show that symptoms have different projected influences on the network's behavior when targeted with alleviating interventions. For example, symptom B1 (Intrusive thoughts) lowers the projected symptom sum score from 10.77 to 8.83. Contrary, symptom C7 (Foreshortened future) merely lowers the projected sum score to 10.01. These results suggest that symptoms may have propelling effects on the decrease of PTSD levels. Instead of lowering the overall sum score by one point when intervening on one symptom, symptom B1 is projected to lower the sum score by two points after an alleviating intervention. Thus, according to NIRA, intervening on B1 could have propelling effects on PTSD levels. Second, we applied aggravating interventions to the Ising model using NIRA (see Figure 6.3; panel B). Here also results show that symptoms have different projected influences after aggravating interventions. For example, symptom C7 (Foreshortened future) has the strongest projected effect on increasing the sum score (from 10.77 to 12.53). In contrast, symptom D4 (Hypervigilance) has the lowest projected effect (increasing the sum score to 11.05).

Therefore, the results suggest the presence of propelling effects when the network is faced with aggravating interventions.

Table 6.1. The 17 PTSD symptoms from the empirical illustration with their corresponding domains.

Domain	Symptom	Node	Prevalence of symptom (proportion)			
			Raw data	*Baseline model*	*Alleviating intervention*	*Aggravating intervention*
Intrusion	Intrusive thoughts	B1	0.77	0.77	0.31	0.97
	Nightmares	B2	0.59	0.61	0.16	0.93
	Flashbacks	B3	0.38	0.41	0.08	0.84
	Emotional reactivity	B4	0.83	0.85	0.41	0.98
	Physical reactivity	B5	0.41	0.46	0.1	0.87
Avoidance	Avoidance of thoughts	C1	0.74	0.77	0.29	0.96
	Avoidance of reminders	C2	0.56	0.55	0.13	0.91
	Amnesia for aspects	C3	0.68	0.7	0.22	0.95
	Loss of interest	C4	0.43	0.46	0.09	0.88
	Feeling distant	C5	0.41	0.47	0.1	0.87
	Feeling numb	C6	0.84	0.84	0.39	0.98
	Foreshortened future	C7	0.24	0.26	0.04	0.74
Arousal	Sleep disturbance	D1	0.64	0.65	0.18	0.93
	Irritability	D2	0.74	0.76	0.27	0.95
	Difficulty concentrating	D3	0.74	0.74	0.27	0.96
	Hypervigilance	D4	0.88	0.89	0.5	0.99
	Exaggerated startle	D5	0.56	0.59	0.15	0.92

The table shows the prevalence (proportion) of every symptom in the raw data, the prevalence as simulated from the original baseline Ising model (without interventions), and the prevalence after every symptom is targeted for an alleviating and aggravating intervention.

To evaluate whether nodes can have different roles in the spread or hinder of symptom activity, we compared the results between alleviating and aggravating interventions (see Figure 6.3; panel C). The results in Figure 6.3, panel C are ordered based on the projected effects from alleviating interventions. Results suggest that alleviating and aggravating interventions have different effects on the same nodes. For example, symptom B1 (Intrusive thoughts) is projected to be the most effective target for clinical interventions, as it has the largest projected effect in lowering PTSD levels after alleviating interventions. However, it is not the projected most effective target for preventive care, as the network's behavior is not heavily affected by an aggravating intervention on B1.

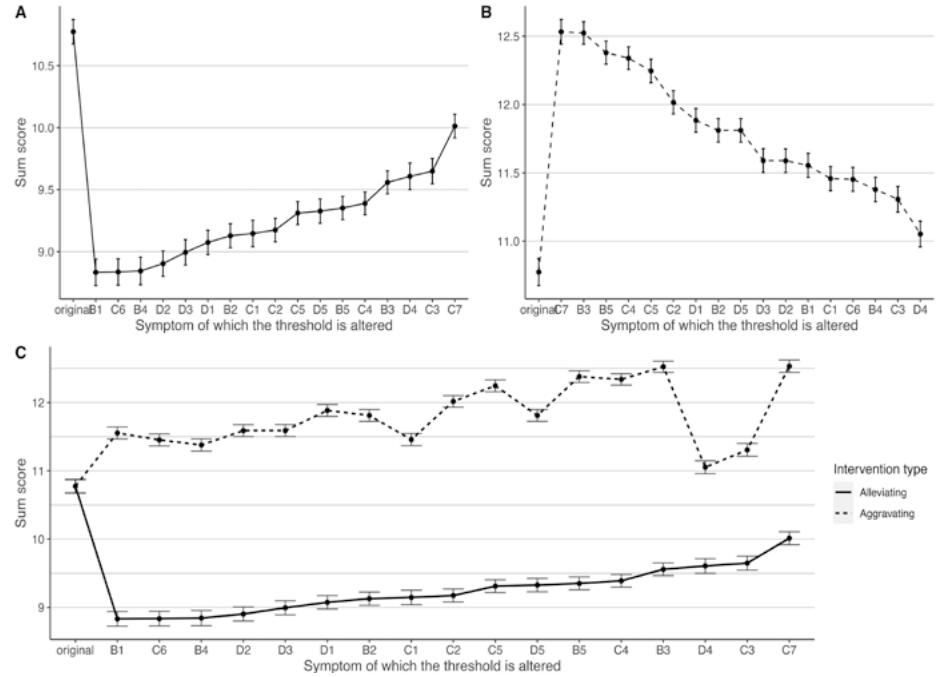

Figure 6.3. Projected effects of NIRA interventions to the PTSD Ising model. Panel A shows results after alleviating interventions (black lines), panel B after aggravating interventions (dashed lines), and panel C compares results from both intervention types. The black dots represent the network's sum score and the corresponding lines the 95% confidence interval. The x-axis shows the symptoms of which the threshold is altered, including the *original* projected sum score of active symptoms, i.e., when data are simulated from the network without altering threshold parameters. Afterward, the projected effects on the network's sum score are shown when data are simulated after every symptom-specific intervention.

Furthermore, we investigated whether the NIRA results could be explained based on the original ordering of threshold parameter magnitudes. For both alleviating and aggravating interventions, we found moderate relations between the threshold values and NIRA outcomes (r=-0.34 and r=-0.31, see Figure 6.4), meaning that threshold values in isolation cannot fully explain the results from NIRA. In other words, projected effects from symptom-specific NIRA interventions also depend on the edge weight parameters in the network.

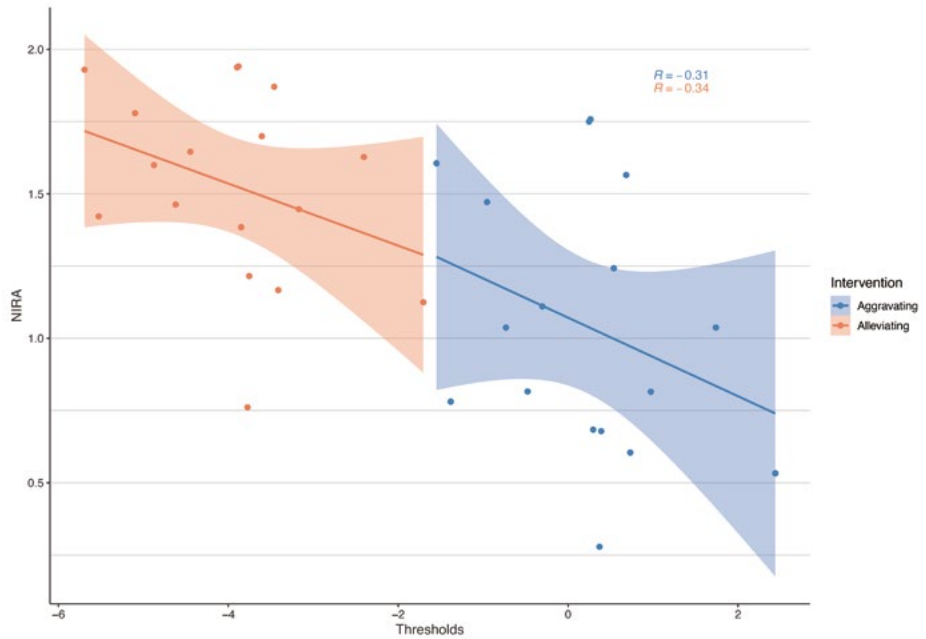

Figure 6.4. The relation between threshold magnitudes and NIRA outcomes after interventions. The x-axis shows the magnitude of the threshold parameters after interventions for both alleviating interventions (black) and aggravating interventions (grey). The y-axis shows the NIRA outcome, computed as the absolute difference between the original sum score of the network and after each intervention. The transparent area represents the 95% confidence interval. The correlations indicate a moderate relationship between the distribution of the threshold parameter magnitudes and their projected effect on the network's behavior after interventions, according to NIRA.

6.3.2 Comparing strength centrality with NIRA

Figure 6.5 shows the results from comparing node strength centrality with alleviating and aggravating interventions from NIRA. The correlation between alleviating interventions from NIRA and strength centrality is $r = 0.51$, and between aggravating interventions from NIRA and strength centrality is $r = 0.43$. Table 6.2 shows all results, including the ordering of PTSD symptoms based on their strength centrality and projected effects from NIRA interventions. These results indicate a moderate to strong relationship between NIRA outcomes and strength centrality.

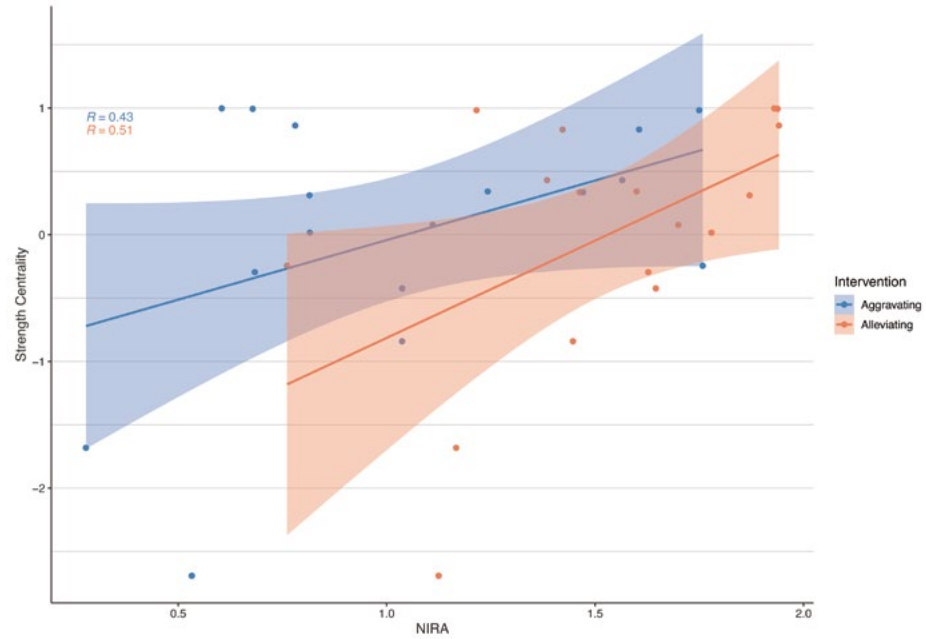

Figure 6.5. Comparing strength centrality with interventions from NIRA. The relation between node strength centrality and projected effects from NIRA interventions for alleviating interventions (black) and aggravating interventions (grey). The area around the lines represents the 95% confidence interval.

Table 6.2. Comparison between strength centrality and NIRA interventions.

Centrality		NIRA			
Strength	*Node*	*Alleviating Interventions*		*Aggravating Interventions*	
1	B4	1.94	B1	1.76	C7
0.99	C6	1.94	C6	1.75	B3
0.98	B3	1.93	B4	1.61	B5
0.86	B1	1.87	D2	1.57	C4
0.83	B5	1.78	D3	1.47	C5
0.43	C4	1.7	D1	1.24	C2
0.34	C2	1.65	B2	1.11	D1
0.34	C5	1.63	C1	1.04	B2
0.31	D2	1.6	C2	1.04	D5
0.08	D1	1.46	C5	0.82	D3
0.02	D3	1.45	D5	0.82	D2
-0.24	C7	1.42	B5	0.78	B1
-0.3	C1	1.38	C4	0.68	C1
-0.42	B2	1.22	B3	0.68	C6
-0.84	D5	1.17	D4	0.6	B4
-1.68	D4	1.12	C3	0.53	C3
-2.69	C3	0.76	C7	0.28	D4

Results from strength centrality analyses and NIRA interventions. Effects from NIRA interventions are calculated as the absolute difference between the baseline network (without interventions) and the symptom sum score after every node-specific intervention from NIRA. Results are ordered from strongest to weakest.

6.4 DISCUSSION

NIRA focuses on the clinical relevance of interventions by studying the projected propelling effect of a symptom-specific intervention on the behavior of the network as a whole. The technique can be used to study the projected effectiveness of different symptom-specific interventions. By altering node parameters instead of node states, NIRA aims to better represent the clinical practice where symptom interventions aim to lower the symptom's activation probability. Furthermore, NIRA distinguishes between alleviating and aggravating interventions. The former interventions could be helpful to determine which symptom may be the most effective target for clinical interventions, the latter to consider which node symptom may be taken into account for preventive care.

As an empirical illustration, we applied the technique to a dataset containing assessments of 17 PTSD symptoms in a sample of participants that experienced the Wenchuan earthquake in 2008. We estimated an Ising model and applied NIRA. Results show that symptoms have different projected influences on the behavior of the network after interventions. These results support the idea that some symptoms have a different effect on the course of psychopathology than others (Borsboom, 2017; Borsboom & Cramer, 2013; Cramer et al., 2016). In the current dataset, symptoms may have (nonlinear) propelling effects on lowering or increasing the network's overall symptom activity levels. If there were no propelling effects, intervening on one symptom would change the sum score with a maximum of one point. However, we found that, for example, symptom B1 (Intrusive thoughts) is projected to lower the sum score by two points after an alleviating intervention. Interestingly, we found that alleviating and aggravating interventions can have different effects on the same nodes. The best target for one type of intervention is not necessarily the best for the other intervention. Since the model is nonlinear and thresholds differ for every symptom, their relative change after an intervention, compared to the value of the other baseline thresholds, is not necessarily the same depending on the type of intervention.

Furthermore, we compared results from centrality analyses using the strength centrality index with results from NIRA in the empirical illustration. We found moderate to large correlations, meaning the most effective targets according to NIRA are related to but may differ from the most central nodes. However, more research is needed for more conclusive results, ideally including more types of centrality values (e.g., eigenvector centrality, a metric that takes into account the number of edges of neighboring nodes and might therefore detect possible propelling effects; Solá et al., 2013).

The presented technique takes a first step in studying the behavior of mental disorders when targeted with symptom-specific interventions using simulations. Due to the pioneering phase of the current research line, the technique has several boundaries and limitations. In this section, we will discuss how the presented technique could be further extended in future research. The first limitation is that the current version of NIRA can only be used with the Ising model (Ising, 1925). This means that binary data need to be at hand or data need to be binarized. Since the Ising model is exponential, results may differ (e.g., effect sizes of simulated interventions would decrease) when using other network models. The same logic could be applied to network models that handle ordinal or Gaussian data, such as the MGM (Haslbeck & Waldorp, 2020) or GGM (Epskamp, Waldorp, et al., 2018). For this, the optimal method to alter node parameters in different models needs to be investigated. Further research could develop equivalent techniques like the one presented here for other network models.

Furthermore, there are several limitations regarding the empirical validity of the presented method. One essential feature of the presented technique is that all

projected effects depend on the assumption that psychopathology behaves in line with the ferromagnetic Ising model (Ising, 1925). This is, of course, almost certainly false. It is possible that current statistical network models, such as the Ising model, do not truthfully represent the complexity of psychopathology. Instead of applying an existing statistical model to psychopathology, one could also try to develop formal models bottom-up, aimed to explain psychological phenomena (Borsboom et al., 2020; Burger et al., 2020; Fried, 2020; Guest & Martin, 2020; Haslbeck, Ryan, et al., 2021; Robinaugh, Haslbeck, et al., 2020; Schiepek, 2003) or psychological capacities (van Rooij & Baggio, 2021). Using the Ising model to simulate the projected influences of interventions, NIRA remains a theoretical exercise, like any other simulation study. Simulation studies teach us what to expect *if* the used model is the true data-generating model (Guest & Martin, 2020). Thus, the problem of the technique's empirical validity is not limited to the presented method. An advantage of these theoretical exercises, such as simulation-based intervention studies, is that they help generate clear hypotheses that can be tested and falsified in an empirical setting (Borsboom et al., 2020). To clinically validate the projected effects of NIRA, experiments need to be done to test whether clinical interventions on the targeted symptoms affect symptom levels as projected.

Relatedly, it is important to note is that effect sizes from NIRA depend on the intervention strength, meaning that propelling effects may disappear with weaker interventions. The impact of clinical interventions is currently unknown, as the empirical validation of the proposed method remains an open question. We chose the current value of two standard deviations as a trade-off between a value that is related to original threshold values (instead of an arbitrarily chosen number), yet also has enough strength to represent an effective clinical intervention. To emphasize that our current choice in the simulations is not the only possibility, we have included a sensitivity analysis in the supplementary materials that shows results after altering threshold parameters with one instead of two standard deviations. In addition, we allow researchers to choose the number of standard deviations that represent interventions when using the *nodeIdentifyR* R package. Future research could focus on the different options to represent symptom-specific interventions in psychopathology networks. One interesting idea has been proposed by Kruis et al. (in preparation), who adhere different values to the symptom variables in the Ising model. A symptom with a solid projected influence, such as insomnia (Blanken et al., 2019), could be given the binary states X = {0, 3), while a symptom with weak projected influence could be given the values X = {0,1). In this case, the insomnia variable will have a stronger influence on the dynamics of the model than other symptoms. Another possibility is to treat the magnitude of the NIRA intervention (i.e., the value with which we alter the threshold parameter) as a random parameter in the population to account for individual differences.

In addition, a strong assumption of NIRA is that it is possible to precisely target one symptom in a clinical environment. It has been suggested that the 'fat fingers' of psychologists do not account for this 'surgical precision' necessary for symptom-specific interventions due to the interrelatedness of symptoms (McNally, 2021). For example, treatment interventions aiming to decrease the 'depressed mood' symptom of a patient may focus on changing maladaptive thought patterns (Burger et al., 2020). Intervening on these thoughts is likely to affect related symptoms such as 'loss of interest' directly. Thus, changes in symptom activity would not result from alterations in the activation probability of *one* symptom but originate from simultaneous changes in multiple symptoms at the same time. It has even been questioned whether psychiatric symptoms are distinguishable entities at an ontological level, on which distinct interventions can be administered (de Boer et al., 2021). Some argue that mental states are too overlapping to be considered suitable intervention targets (Woodward, 2014). In other words, the interdependence of symptoms implies their inseparability, rendering it impossible to separate unique contributions of symptoms (Olthof et al., *under review*). In the current chapter, we do not study the precise effect of one symptom on another specific symptom but study the behavior of the entire network after an intervention. In this way, we consider the interrelatedness of symptoms. In addition, the presented technique could also be administered to multiple symptoms at the same time by targeting various thresholds simultaneously. Another possibility is to combine network models and latent variable models, for example, using *residual network models* (Epskamp, Rhemtulla & Borsboom; 2017, see Figure 6.2 panel d). Here, one assumes that some of the covariations between symptoms are caused by latent variables. Interventions could, in theory, target clustered symptoms simultaneously relative to their factor loadings (e.g., a symptom with a strong (weak) factor loading on the latent variable is highly (weakly) affected by an intervention, meaning its threshold is altered with a large (small) magnitude). Importantly, the directionality of the assumed causal model containing both latent variables and a network structure affects the intervention's effect (Marsman et al., 2018). For example, an intervention on a symptom caused by a latent variable, without connections to other symptoms, will not have propelling effects on the model's behavior. For an extensive discussion on the different causal implications of interventions in network and latent variable models, we refer to the paper by Marsman et al. (2018), specifically, Figure 12.

Relatedly, the presented technique only proposes the *first* optimal intervention target, as the model parameters are likely to change after the applied intervention due to the interrelatedness of symptoms. Therefore, the second symptom that NIRA identifies as most influential is not necessary the best intervention target *after* the first symptom has been targeted. In other words, NIRA does not identify the optimal target for a second intervention. It could be highly interesting to compute a 'hierarchical tree' containing all different pathways of possible symptom-specific interventions.

For example, to study the minimal pathway to clinically meaningful change. Future research could focus on how the computation of such a decision tree could be made mathematically tractable and implemented for psychological network models.

An issue that further complicates matters is the wide-known fact that it is implausible for population effects to translate to individual processes. In other words, the most effective symptom-specific intervention target to lower the population mean of PTSD is not necessarily the most effective target in individuals due to the heterogeneity of psychological processes (Bringmann et al., 2013; Hamaker, 2012; Molenaar, 2004). Ideally, simulation-based idiographic approaches would exist to investigate the most effective intervention target for a specific individual, based on his or her trajectory. One option is using Vector Auto-Regressive (VAR) models (Bringmann et al., 2013). These multilevel models are estimated from intensive longitudinal data (e.g., five measurement moments per day for every participant) and regress all symptom variables on their former measurement moment, allowing for the estimation of unidirectional edges. One possibility to study the effect of interventions in these VAR models is by using *impulse response functions* (IRF), where the system receives an external simulated "shock", or impulse, to study its response over time (Lütkepohl et al., 2015; Yang et al., 2019). IRF is used in economics (see, for example, Inoue & Kilian, 2013), and we hope that psychological research will further expand into that direction. However, until these methods are widely available, cross-sectional models can be a good choice as first explorations of uncharted territories since cross-sectional data collection is efficient in time, money, and patient impact (Spector, 2019).

Until more research focuses on the empirical validity of intervention studies from the context of psychological networks, the optimal representation of interventions in symptom networks remains an open question. However, we hope the presented technique will be a helpful addition to the methodological toolbox for studying the projected dynamics of symptom networks. In this way, computational models and techniques could aid in improving clinical practices and treatment effectiveness.

7

GENERAL DISCUSSION

7.1 MAIN CONCLUSIONS AND SUMMARY

Many people show resilient responses after facing hardship, meaning they can maintain or return to normal psychological functioning (Bonanno, 2021). However, other people develop long-lasting psychological complaints that significantly burden their quality of life, their social environment, and society as a whole (Cuijpers et al., 2012; Lopez et al., 2006). A better understanding of how individual differences in resilience arise may eventually help in improving people's resilience. How can we better investigate the potential mechanisms that give rise to resilience? This question lies at the heart of my dissertation.

In this dissertation, I have argued that we need to *model* the *interactions* between symptoms, risk factors, and protective factors to better represent, understand and anticipate resilience. The italics illustrate the two parts of the proposed approach. First, I argue that computational models and simulations can advance the study of resilience. We cannot expose people to potentially traumatic events, and, therefore, the use of simulations modeling can help to overcome ethical and practical problems in the investigation of resilience. Second, I argue in favor of a complexity approach to resilience that focuses on the interactions between components of the mental health system.

To achieve this, I combined existing complexity models of mental health with simulations modeling to develop a novel framework to investigate psychological resilience. The existing complexity models originate in the *network theory of psychopathology*, which proposes that mental disorders act as complex systems organized in a network of interconnected symptoms (Borsboom, 2017; Borsboom & Cramer, 2013). These symptom networks can be located in a healthy state, meaning that most symptoms are absent, or evolve towards a disorder state, in which many symptoms are activated. By studying the dynamics of these networks and adding simulated *clinical interventions* – which pull the network towards a healthy state – or *stressful perturbations* – pulling the network towards a disorder state, we can investigate how the symptom network may behave under different conditions. In this way, one can investigate, for example, how mental health complaints would evolve under different situations according to the model. As such, one can derive clear, testable, and specific hypotheses on what factors contribute to the system's resilience that can be used for empirical validation (Borsboom et al., 2020; Fried, 2020; Haslbeck et al., 2021; Henry et al., 2021).

In this dissertation, resilience is defined as the situation in which the mental health system is located in a stable and healthy state. In other words, the system will not develop many psychopathology symptoms despite facing adversity. Thus, resilience is not viewed as a component of the mental health system (i.e., a variable in the network)

but as a *property of the system*. As such, the presented framework accommodates the *dynamic* and *multifactorial* characteristics of resilience that have been frequently reported in the last decade's literature (e.g., see: Fritz et al., 2018; Ioannidis et al., 2020; Kalisch et al., 2017, 2019; Rutter, 2012; Xu & Kajikawa, 2018).

Throughout this dissertation, I have shown how the proposed complexity approach to resilience can be applied to statistical network models using simulations. The following section gives a brief overview of how every chapter has contributed to this.

7.1.1 Brief chapter overview

Chapter 2 showed how resilience may be assessed from the architecture of symptom networks by simulating perturbations. The *resilience quadrant* was introduced which organizes symptom networks based on their most likely *state* (healthy or disordered) and *stability* (stable or unstable) against perturbations. An important conclusion is that symptom thresholds play a part in the network's resilience, and as such, the network's connectivity alone does not render enough information. Resilient networks are generally characterized by high symptom thresholds and weak connections between the symptoms. However, different combinations of node and edge parameters can lead to the same resilience level indicating various pathways in which a network's resilience could be improved. Notably, the differences in parameter values that result in different regimes of the resilience quadrant are slight. This potentially explains why resilience is thought to be dependent on complex configurations of factors thought to support resilience.

Chapter 3 presented a formal, complex system of mental health, by showing how risk and protective factors could be integrated into symptom networks. As such, the multifactorial nature of resilience that has been reported in the literature could be accommodated (e.g., see Fritz et al., 2018; Lee et al., 2013; MacBeth & Gumley, 2012; Masten, 2001; Xu & Kajikawa, 2018). Essentially, the chapter proposed that risk and protective factors may alter the architecture of symptom networks, such that they increase or decrease resilience in a non-trivial way. Therefore, resilience can be represented from a multifactorial perspective in which risk and protective factors are interconnected and affect the presence and stability of symptoms.

Chapter 4 expanded the mental health model by including integrated fast and slow mechanisms that affect mental health and resilience. The model was used in the context of psychopathology (fast-changing process) and personality (slow-changing process), in which personality factors alter the architecture of the psychopathology. The applied model connects empirically informed depression and neuroticism networks and shows that simulations from the model result in plausible empirical patterns representing essential phenomena. This chapter was implemented in an

online simulation tool to make the presented study easy to understand and replicate for researchers without a simulations background.

Chapter 5 investigated the relationship between the architecture of symptom networks from individual participants and their symptom evolutions. The chapter concluded that the density of individual networks strongly correlates with the individuals' change in depressive complaints. These complaints either deteriorated or ameliorated over time. Thus, denser individual networks indicate stronger covariances, which is necessarily reflected in the variation of the sum score of the depressive complaints. Although Chapter 2 found denser network to be less resilient, Chapter 5 portrays a novel possibility, namely, the situation in which a higher density in individual networks indicates more fluctuations. However, there are several differences in the networks used in both chapters. Most importantly, different types of network models were used: an Ising network containing only symptoms (Chapter 2), versus a multilevel VAR model containing assessments of both positive affect, negative affect, and depressive complaints (Chapter 5). Furthermore, Chapter 5 did not study how the individual networks would react to simulated perturbations. As such, the conclusions in Chapter 2 are not necessarily a contradiction to the findings of Chapter 5. Nevertheless, Chapter 5 raises the important point that evolutions of cross-sectional models can differ from intra-individual models. Thus, future research should further investigate the resilience of intra-individual models.

Finally, Chapter 6 presented a novel method and corresponding R-package (*nodeIdentifyR*) to study the projected effects of symptom-specific interventions in symptom networks. The proposed method joins a developing novel tradition in which projected influences of symptoms in psychopathology models are studied with simulated symptom-specific interventions (Ryan & Hamaker, 2021; Burger et al., 2020; Castro et al., 2019; Henry et al., 2021; Robinaugh et al., 2016). The chapter offers a novel approach to represent the effect of an intervention by altering symptoms threshold parameters. The effect of a symptom-specific intervention is computed by considering the behavior of the whole network. The method can be applied to empirically estimated symptom networks to identify which specific symptoms would be the optimal targets for therapeutic intervention. Additionally, the method can study which aggravating intervention would have the most unfavorable effect on the network. This could provide information on the vulnerabilities in the network that may have to be considered for preventive care. By taking a complexity approach in which the effects from targeted interventions are studied on the behavior of the whole network, the method anticipates propelling effects that are difficult to identify without simulations.

7.2 MAIN CONTRIBUTIONS TO THE NETWORK PERSPECTIVE OF PSYCHOPATHOLOGY

The research presented in this thesis builds upon the network theory and existing network models (e.g., Borsboom, 2017; Borsboom & Cramer, 2013; Cramer et al., 2010, 2016b; van Borkulo et al., 2014). Network theory has significantly impacted the perception of mental health in clinical practice, and network models offered many methodological innovations (Bringmann et al., 2021). However, several challenges still lay ahead before theoretical and methodological advances are translated to empirical research and clinical practice (Bringmann et al., 2021; Fried & Cramer, 2017; McNally, 2021). I discuss two current challenges of the network theory to which the presented work in this dissertation may contribute.

The first current challenge in the network perspective to psychopathology is how to interpret cross-sectional network models estimated from one assessment occasion (Bringmann et al., 2021; Fried & Cramer, 2017). The edges in these psychopathology networks are estimated from observational data, raising the question of what exactly can be derived from a network's structure. For a causal interpretation of how symptoms affect each other based on the network's structure, it is necessary to assume a dynamic process of how node X affects its neighboring node Y (Dablander & Hinne, 2019). However, this assumed dynamic process is often not made explicit. The concept of node centrality as an indicator of importance or influence in the network has been much debated for this reason (Bringmann et al., 2019; Dablander & Hinne, 2019; Hallquist et al., 2019a; McNally, 2021; Rodebaugh et al., 2018). In this dissertation, the dynamic process that runs over the network model has been made explicit in every chapter by simulating data from the network's structure. Naturally, one may wonder whether the assumed dynamics (e.g., Glauber dynamics in Chapter 2; see the supplementary materials) are a realistic representation of how symptoms affect each other in life. All chapters that used simulations in this dissertation has raised the same question and doubts in every discussion section. However, one can only improve the formulas that govern dynamics when they are explicitly assumed. As such, the current simulations-based approach opens the door for scientific debates, criticism and improvement. Arguably, this is preferable over keeping dynamics implicit, as it clarifies the need to develop better insights into the evolution of symptom networks. Therefore, the simulations presented in this dissertation take a step forward in the interpretability of network models.

The second current challenge is how estimated networks may inform us on the effects of interventions (Bringmann et al., 2021). One of the reasons why network theory was well received in psychopathology is that it provides more possible intervention targets than the traditional latent variable model (Borsboom & Cramer, 2013). Instead of intervening on the unobservable entity "depression", the network theory proposes

that a person's depression level can be diminished by treating specific symptoms (Borsboom, 2017). This aligns with the tools and aims of clinical psychologists (Burger et al., 2020). From a complex systems perspective, one may expect that intervention effects propagate through the network (Blanken et al., 2019). These propelling effects are challenging to foresee without simulations (Henry et al., 2021). Thus, again, dynamics that run over the model have to be explicitly assumed to simulate the projected effects of interventions. The work presented in this dissertation contributes to the network perspective to psychopathology with novel methods that simulate the projected effects from perturbations and interventions.

7.3 A ROADMAP TO FURTHER INVESTIGATE RESILIENCE FROM A COMPLEXITY PERSPECTIVE

Although the work presented here takes a step forward in several areas of the network perspective and resilience research, there are more steps to be made. The sections below describe the most important ones for resilience research and provide a roadmap for future research.

7.3.1 Advancing the presented models

7.3.1.1 Further the development of mathematical and computational models of resilience

This dissertation has adjusted existing, estimated statistical network models to show disordered or resilient behavior when faced with perturbations. In this way, the adjusted statistical network models were used as data-generating mathematical models. This approach has several advantages. First, one can derive *testable hypotheses* from the model's behavior as the simulations add a dynamic process to the network model (Bringmann et al., 2021). For example, the hypothesis that certain symptom-specific interventions have a more substantial effect on lowering depression than interventions on other symptoms (Chapter 6). Second, the approach is data-driven as the statistical models are estimated from data. Therefore, the model's parameters and the simulated data are grounded in empirical observations of symptom co-occurrence. Third, the approach is straightforward: researchers do not require specialized mathematical or programming skills to play around with the model and simulate data (e.g., see the implementation of Chapter 4 in an online, interactive simulation tool). However, the downside of the used approach is that the statistical models used were not designed to explain resilience. The model's behavior is bound to the limitations of the statistical model and, therefore, not always suitable to explain empirical phenomena relevant for resilience research. Chapter 3, for example, discusses the limitation that the influence from risk or protective factors to symptom network parameters does not change over time. Additionally, the PRP model in Chapter 4 is a mere approximation of a *complex adaptive process* in which the model's parameters are updated after responding

to adversity in a resilient or non-resilient fashion. The parameter-updating rules in the model were defined and added manually and not governed by the formulas that simulate the model's behavior. As such, the adaptive and developmental characteristic of resilience is not fully captured.

An alternative strategy to build a formal model is from the ground up, namely, developing a mathematical model that shows resilient behavior (Haslbeck, Ryan, et al., 2019). Specifically, this entails developing the mathematical formulas (e.g., differential equations that describe developmental processes over time) that govern the system's behavior. An excellent example of this approach is the *computational model for panic disorder* (Robinaugh, Haslbeck, Waldorp, et al., 2021). The model successfully shows how interconnected variables such as perceived threat, anxiety sensitivity, and physiological arousal can show vicious cycles of panic attacks and jump towards a persistent disordered state. The advantages of this approach are that the model can be crafted to explain specific characteristics of interest, for example, changing the model's parameters over time to represent the evolution of resilience (Buyalskaya et al., 2021).

However, this bottom-up approach also has some pitfalls. Developing a mathematical and computational complexity model of psychopathology is a lengthy process and relies on advanced mathematical and computational skills (Haslbeck et al., 2021), in which not many psychologists are trained. Furthermore, even though the model is designed to explain empirical phenomena, the computational model's parameters are not grounded in empirical data (Robinaugh et al., 2021). In other words, the model's parameters are chosen based on their plausibility and the behavior that they produce but not estimated from observations. Therefore, the proposed model still needs iterations of empirical validation and a translation towards a statistical model before researchers can use it for their data. The adjustment of existing statistical models could be a first step towards building a formal model from the ground up. One may evaluate what existing models can and cannot do and use them as first approximations. Ideally, there would be a constant theory formation cycle in the scientific community in which experts work together to develop theoretical models, implement them in computational and statistical models, and evaluate their empirical explanatory power and usefulness (Borsboom et al., 2020; Fried, 2020; Haslbeck et al., 2021). Hopefully, this dissertation's thinking tools and straightforward simulation approach can add to a *lingua franca* that connects interdisciplinary researchers.

7.3.1.2 Integrate resilience mechanisms of protective factors

As resilience is highly multifactorial, heterogeneous, and develops over time, finding the right level of analysis that can be used to compare individuals is not an easy task (Infurna, 2021). Researchers have argued in favor of more investigations into the mechanisms of protective factors that account for resilience (Fritz et al., 2018; Sapienza & Masten, 2011; Werner, 2000). Importantly, these protective factors should not be

viewed as the counterpart of symptoms (Bonanno, 2012; Friborg et al., 2009; Masten, 2001). For example, protective variables such as *self-compassion* potentially indicate the presence of resilience mechanisms, which can create an upwards spiral of more positive coping strategies (MacBeth & Gumley, 2012; Pinto-Gouveia et al., 2014). It has been suggested that self-compassion improves emotion regulation, which helps in processing stressors and adversity (Trompetter et al., 2017). Self-compassion may lead to positive cognitive reappraisal and acceptance of adverse situations, leading to more resilience (Allen & Leary, 2010). Additionally, self-compassion may hamper less maladaptive emotion regulation strategies, such as avoidance, thought suppression, and rumination (Barnard & Curry, 2011). These mechanisms would not have been discovered by only focusing on the absence of symptoms.

Ideally, protective mechanisms and symptom evolutions would be integrated into a model of mental health. This dissertation included the study of protective factors into the theoretical framework by proposing that these factors help pull the symptom network towards a stable and healthy state. Chapter 3 estimated a network that included some protective factors, and Chapter 5 studied the relationship between positive affect and depressive complaints. However, the focus was not on the study of resilience mechanisms of protective factors. Future research may use the proposed approach, in which studies that collected more data on protective factors may find more interesting results on potential mechanisms of protective factors. As such, we may broaden our focus from symptom development to developing protective factors and resilience mechanisms.

7.3.1.3 Develop resilience models that reflect intra-individual processes

The presented models and methods in this dissertation may be helpful to study the resilience of different participant groups, such as comparing clinically depressed patients with healthy individuals. In addition, population data are helpful to determine which risk and protective factors may be related to the development of symptoms. However, cross-sectional models cannot assess individuals' resilience or predict specific individual response trajectories. Models that reflect intra-individual processes are necessary to personalize a formal resilience framework. As Chapter 5 showed, the same network architecture may not represent the same symptom evolutions in individuals. The simulations in Chapter 2 thus need to be expanded to simulation and perturbation methods that can be used with longitudinal, intra-individual models such as the networks used in Chapter 5 (e.g., VAR-models). One possibility to study the effect of perturbations in these individual models is by using *impulse response functions* (IRF), in which the network receives an external simulated "shock", or impulse, to study its response over time (Lütkepohl et al., 2015; Yang et al., 2019; Bos, 2021). IRF is used in economics (e.g., Inoue & Kilian, 2013), and hopefully, psychological research will further expand into that direction. Nonetheless, until these personalized methods are widely available, cross-sectional models are a good option to explore uncharted

territories as collecting population data is efficient in time, money, and patient impact (Spector, 2019).

7.3.2 Advancing the presented methods

7.3.2.1 Incorporating different types of adversity in the simulations

In this dissertation, adverse events were simulated with perturbations. These perturbations affected the presence of symptoms (Chapters 2 and 4) or the probability that symptoms occur (Chapter 6). Additionally, perturbations were aimed at the whole network (Chapters 2 and 4) or targeted at specific symptoms (Chapter 6). However, the perturbations did not represent diverse adverse life events, although it is known that different types of adversity have a distinct impact on a person's mental health (Fried et al., 2015). For example, developing a depressive episode after losing a loved one could qualify as a normal response due to the situation's severe impact. In contrast, after a bad day at work, the same response may indicate a more susceptible mental health state. To better represent resilience in response to different adverse events, one could adjust the simulated perturbations to represent different types of adversity. The simulated perturbations used in Chapters 2 and 4 (i.e., the Glauber dynamics, see the supplementary materials) are very flexible and could be altered to represent different types of adversity. For example, one could perturb a few symptoms instead of targeting all symptoms, representing a minor adverse event. Furthermore, one could force several symptoms to be present constantly instead of perturbing symptoms for a brief moment, representing the presence of chronic stressors. Additionally, one could perturb a random number of symptoms to study how the network reacts to different adverse events.

7.3.2.2 Connecting the simulations and perturbations to actual timescales

A related topic for future research is that the simulated perturbations used in this dissertation are not connected to a real timescale. The perturbations in Chapters 2 and 4 mimic a continuous process by only allowing one symptom to change per simulated observation. However, the simulated observations do not reflect an actual timescale, for example, in which one simulated observation would indicate one day. Time is an essential element of resilience as definitions often state that a person has to recover 'relatively rapidly' from hardship to show a resilient response (e.g., Bonanno, 2005; Kalisch et al., 2017; Riley & Masten, 2005). If one wanted to include the velocity of a stress response to resilience assessment, simulations would need to reflect a timescale (e.g., a symptom can only evolve every *x* number of days).

One possible way to handle this is to define resilience in different time horizons (Linkov et al., 2014). For example, setting a cut-off score for the symptom levels that still indicate a healthy state on an *immediate* time horizon (e.g., the same day of the adverse event), *intermediate* time horizon (e.g., a few months after the adverse

event), and *long-term* time horizon (e.g., a few years after the adverse event). One could determine what symptom development or psychological functioning level would qualify as a resilient response for different adverse events and time horizons. Moreover, one could determine resilience by analyzing the speed of recovery from daily, real-life perturbations using observational data (Kalisch et al., 2021; Kuranova et al., 2020). Still, it remains an open question how to connect plausible time scales to simulations that aim to anticipate or predict resilient responses. Hopefully, the simulation methods presented in this dissertation could function as a starting point from which improvements can be developed.

7.3.3 Empirically validating the presented methods and models

The crucial step to go from a complexity perspective of resilience towards a better clinical and preventative practice is to validate the proposed methods and models empirically (Bringmann et al., 2021; McNally, 2021). As discussed before, the models used in this dissertation were not originally designed to explain resilient behavior. Instead, existing statistical models were adjusted to accommodate resilience phenomena described in the literature. Therefore, it is not evident that the simulations in this dissertation will also have extensive ecological validity. For example, it is unlikely that a response to a stressful event will play out precisely as the Ising model proposes. Instead, the main contribution of the work in this dissertation is that it goes towards the formalization of resilience from a complexity perspective. As such, it can produce testable hypotheses, which is a step forward from only estimating network models or offering verbal theories (Borsboom et al., 2020).

Notably, Chapters 2 and 6 generate testable hypotheses appropriate for future research. The novel method presented in Chapter 6 (NIRA) studies which symptom-specific intervention has the largest projected effect on the overall symptomatology level. The method offers the testable hypothesis that the recommended symptom-specific intervention target leads to a higher treatment efficacy compared with other targets. A first step into the empirical validation of this method would be to better understand how treatments play out empirically on a symptom-specific level. Network Intervention Analysis (NIA) offers insight into the sequential process of symptom-specific direct and indirect treatment effects when experimental data are available (Blanken et al., 2019). One could combine NIA and NIRA to validate the simulated symptom evolutions empirically. NIA can be used to investigate whether the propelling effects anticipated by NIRA played out as projected. For example, one could first apply NIRA to a baseline network of a group of patients to identify the optimal treatment targets according to the simulations. After treatment, one could apply NIA to investigate whether the treatment targeted the intended symptoms. In this way, one can start a research line into the empirical validity of simulated intervention methods that may optimize treatment efficacy.

Alternatively, the *nodeIdentifyR* method for NIRA could be extended with an *edgeIdentifyR*. Instead of studying the projected effects of node-specific interventions, one could study the effects of intervening on specific connections between symptoms. The uncoupling of symptoms approximates the aims in clinical practice (Burger et al., 2020). For example, CBT intends to disentangle and break maladaptive cycles between emotions and behaviors that could otherwise lead to self-enforcing symptom evolutions (Rothbaum et al., 2000). Treatments could therefore be conceptualized as trying to diminish the co-occurrence of symptoms, in which the presence of a dysfunctional belief does not lead to a pattern of catastrophic cognitions (Hayes et al., 2015). For example, research into eating disorders has found that symptoms related to a negative body image, such as 'overvaluation of weight', occupy a central position in estimated networks of eating disorders (Smith et al., 2019). The hypothesis is that the connection between such symptoms and maladaptive behaviors, such as binge eating or excessive exercise, would be the most critical links to break (DuBois et al., 2017). It may be challenging to address the symptoms directly, as symptoms related to body image indicate core expressions of eating disorder pathology (i.e., these nodes may have strong thresholds) (Calugi et al., 2021). Instead, CBT may help to block the maladaptive behaviors that follow. A future application of the *edgeIdentifyR* could investigate whether an intervention on the link between such a central node and other symptoms has a substantive projected effect on diminishing the overall complaints.

Furthermore, one could study the empirical validity of the Resilience Quadrant (Chapter 2). To this end, one could follow the longitudinal design of a study that was done by van Borkulo and colleagues (2015). In this longitudinal study, the researchers compared the connectivity of baseline networks between two groups. The first group did not suffer from MD episodes anymore at a later timepoint (remittent MD), while the MD complaints of the second group did not vanish (persistent MD). Symptom thresholds need to be added to the analysis of the network's architecture to investigate whether the architecture of the baseline networks is more resilient in the remitting group than the persisting group. As such, one can study whether the architecture from the baseline networks leads to the differences in symptom development as proposed by the resilience quadrant.

Additionally, to validate the simulation-based approach to the Resilience Quadrant, one may aim to infer the underlying *stability landscape* of network models by constructing their potential landscape using simulations (Cui, Lichtwarck-Aschoff et al., *submitted;* Cui, Olthof et al., *submitted*). If this stability landscape is constructed (for example, for the Ising model network used in Chapter 2), one could compare whether the simulated perturbations render the same underlying stability landscape as the potential landscape.

7.4 FINAL REMARKS

In this dissertation, I developed a framework to investigate psychological resilience from a complex systems perspective using simulations. The framework opens novel possibilities for assessing the resilience of symptom networks and shows different possibilities for the expansion of these models to accommodate behavior from the resilience research literature. However, the framework could also be used in a broader sense in different fields, such as larger behavioral transitions outside of the mental health context. Investigating how susceptible systems are to change, and studying the optimal targets for interventions, could be valuable applications of the proposed methods in other fields. One could investigate how long-term, stable behavioral transitions in society (e.g., the sustainable energy transition) could be achieved using the proposed framework. For example, to anticipate otherwise unforeseen secondary effects from targeted interventions.

This dissertation was written in the middle of a global COVID-19 pandemic. For me, the pandemic further displayed the need to embrace a complexity approach. A complexity approach is fundamental to understanding how people adapt to adversity in a dynamic and interconnected world. Societies are becoming increasingly interdependent and will face urgent and global crises over the next decade (such as the climate crisis). Adapting a modeling approach that studies different scenarios helps understand how different interventions may play out, as these cannot be understood in isolation. We may isolate characteristics of people in research laboratories, but the pandemic showed how difficult it is to isolate people in the real world.

&

SUPPLEMENTARY MATERIALS

A

SHORT INTRODUCTION TO R

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A.1 INTRODUCTION

This supplementary chapter aims to provide the reader with the programming background and skills necessary to independently carry out analyses of the network approach to psychopathology. To date, the network approach is almost uniquely implemented in R, making it an essential tool for carrying out psychological network analyses.

A.1.1 The R environment

A.1. 1. 1. Why use R?

Using R for psychometric analyses is no longer reserved for specialists or extremely enthusiastic methodologists. During the past decade, psychometric analyses in R have expansively increased, making it, currently, the norm for doing general psychometric analyses (Mair, 2018). There are good reasons for this: R is a powerful programming language for statistical analyses, data visualization, data mining, and general programming. Furthermore, R is freely available, open source, and is accompanied by a large and lively community. Many statistical analyses, such as the ones discussed in this book, are implemented in R packages, making the use of novel statistical methods easy.

A.1.2 Installing and setting up R and RStudio

We suggest installing two different programs for using R: the base program R itself, as well as an integrated development environment (IDE): RStudio. R is the base programming language, which can be operated through the terminal or command prompt. The popular IDE RStudio presents a clear and easy-to-use environment to work in, which includes in addition to the R console itself also a plain text editor for editing R code, several useful panes for displaying plots, help files, loaded objects, and more. While it is possible to carry out all analyses presented in this book without using RStudio (e.g., by directly working in the computer terminal), we suggest using RStudio and assume it is used throughout this book.

Please note that R and RStudio need to be installed separately from different websites, and that these programs have to be updated separately as well. The latest version of R can be installed from https://www.r-project.org/, and the latest version from RStudio can be installed from https://rstudio.com/products/rstudio/download/. It is advisable to always work with the latest version of both programs.

After installing both R and RStudio, you can open RStudio to get started. It can then immediately be seen that the RStudio program consists of four main panes:

Console	The console pane processes commands, meaning that you can enter and execute commands here. However, we suggest using the Source pane for executing (and saving) your commands. The console is similar to the terminal of the R base program and it will not allow saving your script.
Source	The source pane is a plain text editor, meaning it shows plain text in the form of numbers, symbols, and letters. Here, you can write and edit your code, as well as save it in the form of a script. It is highly recommended to work from your script and send your commands to the console, instead of directly working from the console.
Plots/Help	This pane has two functions. The first is to show graphical output, for example, figures such as scatterplots or barplots created from your code. Graphical output can be saved in several formats, such as .pdf, .tiff, or .jpeg. The second function of this pane is to show you documentation of functions (functions will be further discussed in Section A.4). Any function in R is accompanied by documentation. Documentation gives information on what functions do, which arguments can be specified, and what the output will be. Many manuals also include example code on how to use the function. Documentation for every function can be found under the help tab or by using the question mark followed by the name of the function `?name`. For example, running the following command `?mean` gives the documentation for the function which calculates the mean of an object.
Workspace	The workspace shows which objects are currently loaded in your environment. Objects can consist of, for example, loaded data sets or created objects such as matrices and vectors. Please note that it is not recommended to save your workspace when closing RStudio, as in every future session the same objects will be reloaded and this may create issues in new scripts or overwrite functions. In addition, always loading your objects from your script is better practice for reproducibility.

It is recommended to have the console and source panes on top, since they are the most important, and plots and workspace panes below (see Figure A.1). Pane layouts can be set with *Tools* > *Global Options* > *Pane Layout*. In *Tools* > *Global Options* > *Appearance* the theme of RStudio, including background colors and text colors, can be changed.

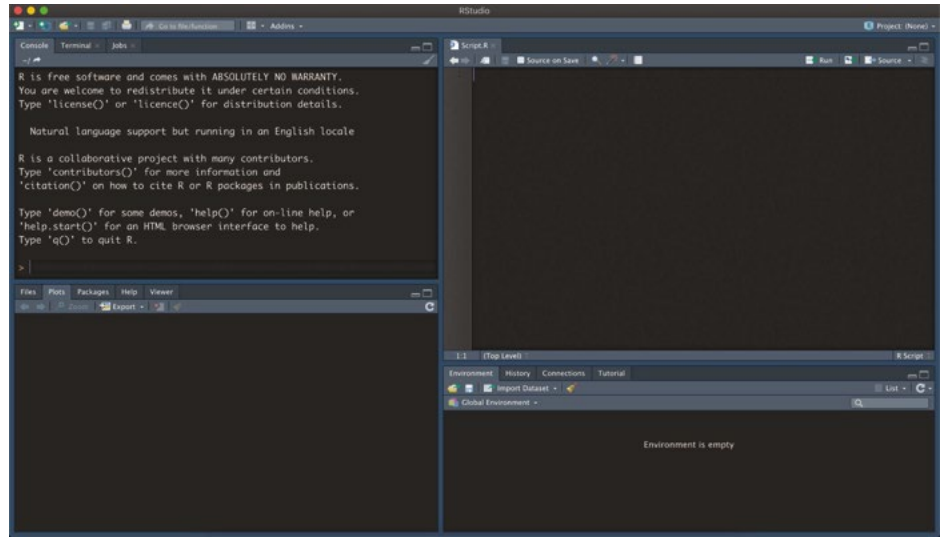

Figure A.1. Example of RStudio with the four panes ordered in the recommended setup, clockwise from top left: the R Console pane, the Script pane, the Workspace pane, and the Plots/Help pane. Note that the color of RStudio is set here according to a theme, which can be set using *Tools* > *Global Options* > *Appearance*.

A.2 BASICS OF R PROGRAMMING

This section will discuss some of the basics of R programming, starting with how R can be used as a calculator, and ending with how to write the first forms of an R script that can be saved and loaded later.

A.2.1 Using R as a calculator

To start programming in R, experiment with the console pane. For example, write the following command, followed by pressing enter:

```
1 + 1
```

R will now return the number 2, telling you that the sum of 1 and 1 equals 2. The full output in the console is:

```
[1] 2
```

The 2 refers to the answer of our question ('what is 1 + 1?'). The [1] indicates that the first element of the answer is the number 2. This is specific to R: R will often return vectors, series of numbers, even if the vector is only one element long (i.e., a single number). So, in full, this output tells us that a vector is returned, and that its first element equals 2. For now, you can ignore the [1] completely.

Next, try to enter:

```
1 +
```

followed by pressing enter. Now, something else happened: the console prompt > changed into +. This is because R is still expecting input. If you type another number and press enter the command will finish and output will be returned. Alternatively, if you press escape the command will be cancelled, allowing you to enter new commands into R.

Of course, R can do more than just add numbers. Several other operators work as might be expected. For example, * can be used to multiply numbers, / can be used to divide numbers, ^ can be used to raise numbers to some power, and brackets (and) can be used to group commands and give precedence over evaluating some commands first. In addition, there are several *functions*, which will be explained in more detail later, that can be used for mathematical operations: `sqrt(...)` computes a square root ($\sqrt{...}$), `exp(...)` computes the exponential function `log(e...)`, `log(...)` computes a logarithm ($ln(...)$), and so forth.

A.2.2 Writing R code in a script

While the console is the pane that actually accepts R commands, as well as the pane in which most output is returned, it is highly recommended to never write code in the console pane directly. Instead, R code should be written in an R script such that the commands can be saved and used later again. In addition, scripts allow for more complicated sequences of R commands to be written. Often, you need to evaluate many commands sequentially, e.g., commands to read, transform, plot, or analyze data. Furthermore, saving code in scripts makes your code reproducible for other researchers.

To create an R script, select *File* > *New File* > *R script.* Immediately also save the script using *File* > *Save As*. Always use the R extension to save R scripts. Now, R commands can be written in the script pane instead of the console pane. Sending commands from the source pane to the console is done by selecting the relevant code and pressing "Run", or alternatively, pressing `control+enter`/ `cmd+enter`. This sends the selected commands to the console, where they will be processed.

A.2.3 Comments

Including comments in your script helps other researchers, or your future self, understand your code. Comments are added by using the hashtag # before writing code; any line of R code will no longer be evaluated from the moment # is encountered. These comments can then be used to explain what the purpose of the code is or why it is added. Alternatively, comments can be used to omit part of the code temporarily

(this is termed 'commenting out' some code). Tutorial Box 1 gives some examples of how a comment can be used.

Tutorial Box 1. Placing comments in the code to clarify code.

Any code past a # symbol will not be evaluated by R. For example, the code:

```
1 + 1 # + 1
```

will return 2, not 3, as the code 1 + 1 is evaluated, and the last bit is not. As such, the # can be used to clarify code. For example, a clarification can be added after a line of code:

```
1 + 1 # This sums the numbers 1 and 1
```

or before a line of code:

```
# Sum the numbers 1 and 1:
1 + 1
```

We recommend to use comments very liberally in the code. For example, it is not uncommon for almost every line of R code in an analysis script to be accompanied by a comment.

A.2.4 Programming style and coding conventions

Carrying out statistical analyses in R implies writing code. This means not only having to learn the correct programming commands for conducting specific analyses, but also learning rules on what code should look like. The set of rules that determine the coding format are called coding conventions, which are related to general programming style. Just like there are guidelines for how to write research papers (e.g., American Psychological Association, 2020), many guidelines also exist for how to write clear code. While it is never mandatory to adhere to a specific coding convention, writing code according to coding conventions does greatly increase its readability and clarity, making it easier to share with other people and to maintain code over time.

Although there is no clear best style guide for programming in R, the "*tidyverse style guide*" by Hadley Wickham is often viewed as one of the most important ones[10]. It should be noted, however, that style guides are inherently opinionated, and therefore arguments can be made in favor and against every element included in any style guide. This book will not rely on strong rules on particular programming style. However, we would like to make readers aware that style guides exist, and encourage thinking about the format of code when doing analyses in R.

10 https://style.tidyverse.org/

A.3 BASIC R DATA STRUCTURES

While it certainly can be nice and useful to write mathematical expressions in R, the output of such expressions has to be stored such that it can be used in later commands. In addition, when data are analyzed, they need to be stored inside R as well, such that they can be called later. Saving the output from commands or storing data in R can be done by using *objects*. This section discusses objects in more detail.

A.3.1 Assigning objects

Objects can contain anything in R. For example, a single number can be stored in an object, but also more complicated data structures and books worth of text. The <- operator is used to store values into objects. For example, the following statement saves the number 1 in the object a:

```
a <- 1
```

Now, instead of writing 1, the object a can be used. For example:

```
1 + a
```

will again return the number 2. Alternatively, the = operator also functions to store values into objects. We do not recommend using =, however, because <- is unambiguous, explicating the left part becomes what is on the right part, while the = operator is ambiguous. Furthermore, = cannot be used within function calls to assign objects.

R expressions that are not stored into an object are printed in the console. When entering a command where an expression is saved into an object, the result of the object is not printed in the console. To see the value of the object, you need to run the name of the object into the console. For example, the following statement evaluates `1 + 1 = 2` and stores the result into the object b, but does not print the result:

```
b <- 1 + 1
```

To get the result, we can ask R to print the result with `print(b)` or just by typing `b`. All currently loaded objects are listed in the workspace pane. When quitting R, you will be asked if you would like to save the objects in your workspace. As emphasized above, it is recommended to never do this.

A.3.2 Naming objects

You can use any combination of letters, numbers, and some symbols, such as the underscore _, to form object names, as long as the object does not start with a number. It is important to give your objects informed names, which describe the content of your object. In this way, it will be easier for other people to read and understand your code. Various conventions and standards exist regarding object naming. Object names

in R are *case sensitive*: `object`, `Object`, and `OBJECT` are different objects. The *tidyverse* style guide recommends to only use lowercase letters, numbers, and underscores. Underscores should be used to separate words, for example, `data_wave_1` instead of datawaveone. Another frequently used style, without using underscores or other operators, is *lowerCamelCase*. Here, the first letter of the first word is lowercase, and the following first letters of words are uppercase. For example: `sampleSize`, `rawData`, and `nMales`.

A.3.3 Object modes

Objects in R can be of different types, called object modes. There are three main object modes for the standard output in R (a vector): numeric, character, and logical. Tutorial Box 2 gives examples of each of these object modes. Numeric objects store numbers, on which you can apply mathematical operations. Character objects, also called strings, store any form of text between tick marks (which can be double tick marks, ", or single tick marks, '). You cannot apply mathematical functions on character objects, since character strings are not numbers (even if they look like numbers). Logical objects indicate if something is true or false, and consist of the Boolean objects `TRUE` or `FALSE`. Commonly used shortcuts you may see in code are `T` and `F`. However, we strongly advise not to use these shortcuts. This is because F can be overwritten and stored as another object, for example `F <- 1`. In this case, F no longer refers to `FALSE` but to the number 1. This is problematic, as R sometimes interprets the number 1 as `TRUE` without warning. When a logical statement is preceded by an exclamation mark (!) the logical result is reversed (`!TRUE` becomes `FALSE` and `!FALSE` becomes `TRUE`). Logical modes are used in two ways: in functions, to assign logical modes to arguments, and in performing logical tests.

Tutorial Box 2. Examples of three object modes that can be used in R: numeric, character, and logical.

The following code creates a numeric object:

```
numericObject <- 1
```

This object can subsequently be used as a number:

```
numericObject + 1 # This will return the value 2
```

The following object is a string and not a number:

```
characterObject <- "1"
```

This object cannot be used as a number:

```
characterObject + 1 # This will result in an error.
```

Finally, we can also store a logical object:

```
logicalObject <- TRUE
```

Interestingly, this object can be used as a number, as `TRUE` also refers to `1` and `FALSE` to `0`. In addition, the logical values are also returned when asking R a logical test. For example:

```
1 == 0 # This will return the message FALSE
```

A.3.4 Missing data

Missing data are encoded in R with `NA`, which means 'not available.' Missing data are handled differently for different functions. To find the right argument for handling missing data in the function you are using, review the documentation for that specific function using `?`.

A.3.5 Vectors

A vector is an object that stores multiple values. These values can include numbers, but also characters such as letters, or missing data (encoded with `NA`). To assign a series of values to a vector, you can use the combine function `c(...)` by simply adding the series you want to combine into a vector. Every element of the series is separated by a comma. A second way to create a vector, is to use the colon : to create a series of successive numbers. Vectors can also be indexed using square brackets (`[` and `]`), which means selecting a certain cell or collection of cells from the vector. This can be used to check the values of these cells, to use them for analyses, or to change them. Tutorial Box 3 gives some examples of how vectors can be used.

Tutorial Box 3. Examples of vectors in R.

The combine function `c()` can be used to create a vector. For example, the following code will create the vector `1 2 3 4 5` :

```
numericVector <- c(1, 2, 3, 4, 5)
```

Because this is an integer sequence, the same vector could also be formed using:

```
numericVector <- 1:5
```

A vector can also contain missing elements, which are encoded as `NA`:

```
vectorMissing <- c(1, 2, 3, NA, 5, 6, NA, 8, 9, 10)
```

Many functions in R tend to return errors when elements of a vector are missing. For example, the `mean( )` function can be used to compute the mean of a vector, but using it on a vector with missing elements will lead to an error:

```
mean(vectorMissing) # Results in an error
```

Instead, missing data must be handled in a way that is acceptable for the function used. For the example above, we could remove all missing elements using `na.omit( )`:

```
mean(na.omit(vectorMissing))
```

or an argument of the `mean( )` function can be used to do the same:

```
mean(vectorMissing, na.rm = TRUE)
```

Always refer to the help file of a function for information on how to handle missing data. Finally, vectors can be indexed using square brackets that follow the name of the vector. The square brackets can contain integers indicating the elements of the vector (starting with `1`), or a logical vector of the same length as the original vector with `TRUE` indicating an element should be returned. For example, `vectorMissing[1:3]` selects only the first three elements of the vector and `vectorMissing[!is.na(vectorMissing)]` selects all elements that are not `NA`.

A.4 FUNCTIONS AND PACKAGES

The introduction of vectors also introduced the concept of functions. A function is a small program: it takes input, does something, and gives output. For example, the combine function `c(...)` takes some values, combines them, and gives a vector consisting of those values as output. Some other examples of common functions are `mean(x)`, `sd(x)`, and `sum(x)` to compute the mean, standard deviation, and sum over elements of a vector called `x`.

Functions always have the same form, namely, their name, and then the corresponding arguments within brackets: `name(argument, argument, argument, ...)`. Some arguments have default settings, meaning that the parameters of that argument are set. This makes the functions more generic to use, however, you can always change the parameters of every argument when using functions.

To know which arguments can be provided, and which default arguments apply, every function in R is accompanied by documentation. Reference cards also give a good overview of R functions for frequently used analyses, which can be found online. Furthermore, you can use online search engines and the R community to find the exact function names and arguments for the analyses you want to execute. You can also write your own functions using `function()`. However, this is part of advanced programming skills and will not be discussed throughout this book. Several freely available online resources on this topic exist.

Packages are extensions contributed to R containing extra functions. Developmental versions of R packages can often be found on Github, and stable versions of R packages are commonly stored on the Comprehensive R Archive Network (CRAN). Several packages are necessary for carrying out the analyses described in this book. All packages need to be installed once by using `install.packages()`[11]. For example, the following command installs the package bootnet.

```
install.packages("bootnet")
```

This may take a long time, and only has to be run occasionally, to ensure the package is up to date. It is not recommended to leave a call to `install.packages(...)` in an R script (or if it is included, include a comment sign # before the call so it is not always evaluated). After installing a package, the package also needs to be loaded using the function `library(...)`. For example, the bootnet package can be loaded with:

```
library("bootnet")
```

Alternatively, the function require() can be used. This makes all exported functions from the bootnet package available to the user. Contrary to `install.packages(...)`, the `library(...)` command does have to be used at the beginning of every script that uses functions from a package.

A.5 ADVANCED OBJECT STRUCTURES

We already discussed different modes of objects in R and vectors that combined several objects. Typically, data in R are presented in more advanced structures than vectors. For example, networks can be encoded using two-dimensional matrices, and data are

11 Sometimes R may struggle to install an R package and return an error. If R asks if you want to install a package from source, it is best to answer 'no' unless you have your system set up to install packages from source. Answering 'no' does not stop installation but rather continues with installing pre-compiled packages from CRAN, which is easier. Most R packages depend on other R packages, which should be installed automatically. Sometimes, however, this does not work. Whenever R returns an error that some package is not installed or cannot be loaded, try installing that package first. Sometimes then a new error may be returned pointing out a different package that needs to be installed.

typically stored in a form of a matrix, in which columns can have different modes (data frames). This section will introduce these more advanced object structures.

A.5.1 Matrices

An important function when doing network analyses is the `matrix()` function. Technically, a matrix is a vector with two dimensional attributes. Rows indicate horizontal lines of cells, while columns indicate vertical lines of cells. The first argument of a matrix is a vector (i.e., the data) to fill the matrix with, the second argument the number of rows, and the third argument the number of columns. Indexing in matrices can be done using square brackets, where the first value indicates the row number and the second value the column number, separated by a comma. Some examples of how to use matrices are shown in Tutorial Box 4, and documentation for the matrix function can be found with `?matrix`.

Tutorial Box 4. Example code for creating and indexing matrices.

The matrix function can be used to create a matrix:

```
myMatrix <- matrix(1:9, nrow = 3, ncol = 3)
```

Note that the matrix is filled columnwise. To fill the matrix rowwise, we can instead use:

```
myMatrix <- matrix(1:9, nrow = 3, ncol = 3, byrow = TRUE)
```

Next, we can index the matrix using square brackets. For example, `myMatrix[1,2]` selects the cell at row 1 and column 2, `myMatrix[1:2,1:2]` select the block with the first two rows and columns, and `myMatrix[1:2, ]` selects the first two rows and all columns.

A.5.2 Lists

Lists can consist of any (combination of) data modes. Lists are like coat racks that can store any type and combination of object modes, even other lists! For example, numeric matrices and vectors consisting of characters can be combined into a list. The first element will be the matrix, while the second element will be the vector. Every element of a list can be named. To index from a list, the `$` operator or double square brackets (`[[` and `]]`) can be used. An example can be seen in Tutorial Box 5.

Tutorial Box 5. Examples of constructing and indexing lists.

We can create a list with two objects, one vector consisting of character elements, and one matrix consisting of numeric elements, with the following code:

```
myList <- list(characterVector = c("a","b","c","d"), numericMatrix = matrix
          (data=c(1,2,3,4), nrow = 2, ncol = 2))
```

To confirm that the list consists of two objects, one character vector and one numeric matrix, we can use the structure function with `str(myList)`. To index the list, we can use double square brackets. For example, the following selects only the first element of the list:

```
myList[[1]]
```

We can do the same by using the name of the element:

```
myList$characterVector
```

Finally, we can also index elements of lists. For example, the following selects the first element of the first object of the list:

```
myList[[1]][1]
```

A.5.3 Data frames

Data frames are the most used objects for storing data sets; most data sets, such as data sets imported from the statistical program SPSS, will be represented as data frames in R. Technically, a data frame is a list in which each element is a vector of the same size. This allows the data frame to also be represented (and indexed) as a matrix. Data frames can store different variables, such as numeric variables, indicating scores on a questionnaire, but also characters, such as "`male`" and "`female`". Since they are technically a list, you can index data frames using the `$` operator. However, you can also index data frames in the same way matrices are indexed. Tutorial Box 6 shows how a data frame can be created.

Tutorial Box 6. Working with data frames.

We can create a data frame with two variables indicating a participant's score and gender, consisting of a numeric vector and a character vector:

```
myDataFrame <- data.frame( score = c(3, 6, 2, 4), gender = c("male",
               "female", "other", "female"))
```

To index the data frame, the `$` operator, single square brackets and double square brackets can be used. For example, all these commands will index the second column (gender):

```
myDataFrame$gender
myDataFrame[,"gender"]
myDataFrame[["gender"]]
myDataFrame[,2]
myDataFrame[[2]]
```

A popular R package for manipulating data frames is the *dplyr* package (Wickham et al., 2021). The *dplyr* package contains several powerful functions for manipulating data. For example, the select function can also be used to select a variable:

```
select(myDataFrame, gender)
```

and the `group_by` and `summarize` commands can be used to compute something for every level of one or more grouping variables:

```
summarize(group_by(myDataFrame,gender),
mean= mean(score))
```

This code computes the mean for every level of gender. The dplyr package exports a handy pipe operator, `%>%`, which can be used to express, for example, `f(g(x))` as `x %>% g %>% f`, in which `x` is some R object and `f` and `g` are some R functions. This can be used to write chains of commands easier (reading from left to right instead of from inside to outside):

```
myDataFrame %>% group_by(gender) %>%
      summarize(mean = mean(score))
```

A.6 WORKING WITH DATA IN R

Now that you are familiar with the way R works, it is time to start looking at real data. To do this, data need to be loaded into R as an object, after which it can be used for analysis.

A.6.1 Working directory

The working directory is the folder on your computer in which R is currently operating. This means that your data will be loaded from this folder, and any output created (e.g., new data and plots) will be saved to this folder. You can request your current

working directory with the function `getwd()`. A common error that can occur is that a file is requested which is not located in the working directory. To solve this issue, you need to change your working directory or add the needed (data)file to your current working directory. To set your current working directory, you can use the function `setwd()`. Another way to set your working directory is by clicking Session Set Working Directory Choose Directory. This will allow you to set your working directory to a location of choice. Finally, as also shown in Figure A.2, you can also set your working directory by clicking *Session* > *Set Working Directory* > *To Source File Location*. This sets your working directory to the same folder as where your current script is saved, which is convenient, since this allows you to easily load and save objects, (data)files, and scripts within the same folder.

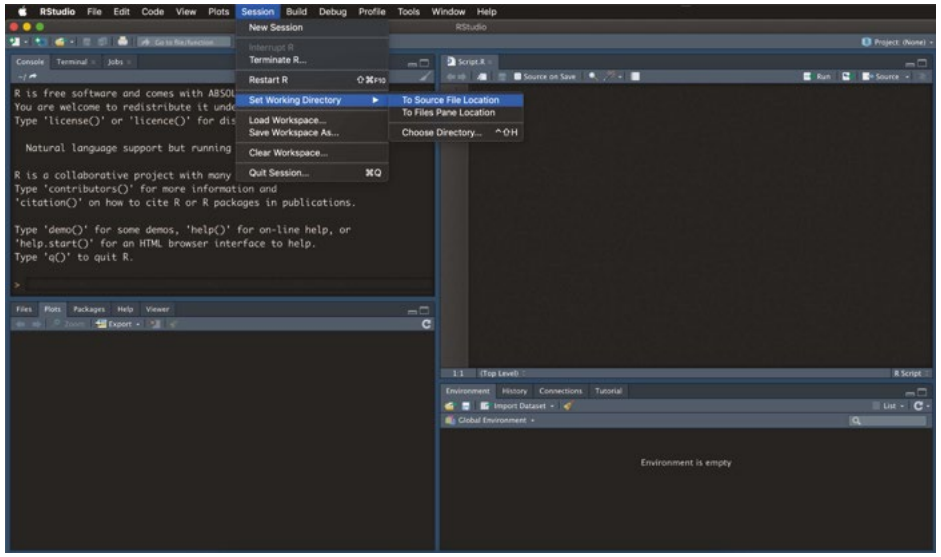

Figure A.2. Setting up the working directory.

A.6.2 Importing data into R

After the working directory is correctly specified, there are several ways to load data sets into R. First, data sets can be loaded into R from different sources (e.g., CSV, SAS, SPSS, Microsoft Excel) by clicking *File* > *Import Dataset*. This option will in addition provide you the code to import data, which you can also use directly. Second, datasets can be loaded into R directly, by using a command to read your data. The most common format to read data into R is the Comma-Delimited (CSV) format. Please note that reading SPSS or Microsoft Excel data files into R requires installing and loading dedicated R packages. Tutorial Box 7 shows examples of code that can be used to read data into R.

Tutorial Box 7. Importing data from plain text files and SPSS files.

If data `mydata` is stored in a plain text file with the extension .csv and located in the same directory as the script, then, after setting the working directory to the same location as the script with *Session* > *Set working directory* > *To source file location*, the data can be loaded into R and stored in an object called data with:

```
# Read a CSV data file into R

Data <- read.csv("mydata.csv")
```

Possible, some arguments need to be used to specify how exactly the data are stored. See for more information `?read.csv`

If the data mydata are instead stored in an SPSS file with the extension .sav, the following commands can be used to read the data and store them in an object called data:

```
#Read an SPSS data file into R

install.packages("foreign")

library("foreign")

data <- read.spss("mydata.sav", to.data.frame=TRUE)
```

Both the functions `read.csv()` and `read.sav()` return the data in a data frame.

A.6.3 Correlation & covariance

After the data are loaded into R, they can be used for statistical analysis. For example, the data could be used to estimate a correlation matrix, which will play an important role in some of the analyses discussed in this book. The function `cor()` computes a correlation from a data frame (or any other type of numerical data) and the function `cov()` computes the covariance. The argument method selects the method for computing the correlation or covariance. The default is using Pearson correlations, (`method = "pearson"`), but other options include Spearman (`method = "spearman"`), and Kendall (`method = "kendall"`) correlations.

A.7 CONCLUSION

This chapter introduced the reader to basic concepts of the statistical programming language R. However, it can be noted that R is a very extensive programming language, and the full extent of programming in R cannot readily be captured in a single chapter. For example, we did not discuss actual programming in R (such as using *if-statements* and *for-loops*), how to write functions, how to write efficient R code, or how to do more complicated statistical analyses. As R is a very popular open-source programming language, there is a wealth of freely available guides available online that teach these more advanced topics of programming in R for the interested reader.

B

SPANISH INTRODUCTION TO THE NETWORK APPROACH: PSICOPATOLOGÍA COMO RED CAUSAL COMPLEJA DE SÍNTOMAS

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ABSTRACT

El modelo de la psicopatología como red de síntomas propone centrarse en las interacciones dinámicas y causales entre los síntomas constitutivos del problema clínico. La idea principal es que la activación de un síntoma clínico lleva a la activación de otro síntoma vecino. Las conexiones entre ellos pueden ser biológicas, psicológicas o sociales. Los trastornos mentales son concebidos como estados estables alternativos de redes de síntomas fuertemente conectados. Esto permite un modelo explicativo común para todos los trastornos mentales, un modelo integral de psicopatología. A pesar del éxito de este nuevo camino metodológico, la mayoría de la información relevante se encuentra publicada en inglés. En este artículo, se presenta, en idioma español, la teoría de la psicopatología como red de síntomas y su modelo, su relevancia para la investigación, docencia y práctica clínica de la psicología y la psiquiatría, a los fines de incrementar su difusión y diseminación.

INTRODUCCIÓN

El diagnóstico constituye uno de los primeros pasos de la atención clínica. Existen diversas perspectivas sobre el diagnóstico en el campo de la psicología clínica y la psiquiatría. Las clasificaciones de los problemas clínicos se proponen según variados autores y modelos teóricos. Esta diversidad se suma a las dificultades en los diferentes contextos en los que el diagnóstico y la evaluación tienen lugar: la comunicación con los pacientes, el trabajo con otros profesionales de la salud (médicos de distintas especialidades, enfermeros, trabajadores sociales, terapeutas ocupacionales, etcétera) y la relación con organismos de salud (ministerios, secretarías, universidades, hospitales y centros de investigación o asistencia). Cada contexto presenta sus particularidades y desafíos específicos. Por ejemplo, el derecho de los pacientes a conocer su diagnóstico y las opciones para tratar su problema clínico presenta características diferentes a las necesidades de establecer definiciones operativas por parte de centros de investigación que busquen determinar los problemas clínicos frecuentes de determinada sociedad. En el ámbito de la investigación, resulta sumamente útil y necesario contar con definiciones operativas de los problemas clínicos que permitan comparar estudios de prevalencia, realizar investigaciones psicopatológicas, seguir la evolución de los cuadros, llevar adelante estudios de etiopatología, diseñar y estudiar pruebas psicométricas, y, finalmente, evaluar el impacto de intervenciones psicológicas, biológicas y sociales en el corto, mediano y largo plazo. Por su parte, el trabajo interdisciplinario en el contexto institucional, como lo constituye, por ejemplo, un hospital universitario, requiere la comunicación entre profesionales con diferentes conocimientos, habilidades y destrezas, marcos teóricos, y perspectivas sobre la asistencia. En ese contexto, resulta necesario contar con consensos sobre las definiciones de los problemas clínicos que se deben asistir.

Los sistemas diagnósticos operacionalizados (DSM) tienen el ambicioso objetivo de definir los problemas clínicos de acuerdo a consensos basados en la investigación empírica existente actualmente. Se centran en la descripción de los problemas clínicos sin adentrarse en hipótesis explicativas, aunque implícitamente suponen un modelo biomédico, al que se hará referencia oportunamente. Estos sistemas pretenden brindar definiciones para la investigación, la docencia y la práctica clínica que superen los interminables debates entre diferentes autores y escuelas y, efectivamente, son una herramienta provisional y necesaria para realizar estudios epidemiológicos, evaluar intervenciones en ensayos clínicos, difundir información para la prevención, detección y tratamiento de diversos problemas de salud mental, entre otras tareas esenciales. Sin embargo, una de sus ventajas es también un grave problema: carecen de una teoría explicativa. Como se ha dicho sobre el DSM-5, resulta "más un diccionario descriptivo que un manual de psicopatología" (Echeburúa, Salaberría, y Cruz-Sáez, 2014). Necesariamente es así porque el desacuerdo reina en el campo de la salud mental: no se logra un consenso en el nivel teórico, sino solamente en el nivel descriptivo, y muchas veces ni siquiera en este nivel, dado que la descripción difícilmente puede separarse de la explicación.

En este mar de debates y controversias, se presenta una teoría (Borsboom y Cramer, 2013) que tiene la ventaja de guiar tanto la conceptualización de los trastornos psicológicos como su tratamiento (Hayes, Yasinski, Barnes, y Bockting, 2015). Se trata de un modelo que podría llegar a transformar el campo de la psicopatología de muchas maneras, al tender un puente entre las necesidades clínicas y científicas (McNally, 2016). En el mundo de habla hispana, son escasos los estudios realizados desde esta perspectiva (Blanco et al., 2019; Fonseca-Pedrero, 2018; Romero-Montes, Sánchez-Chávez, Lozano-Vargas, Ruíz-Grosso y Vega-Dienstmaier, 2016; Vega-Dienstmaier, 2015), por lo que este artículo se propone contribuir a su difusión entre investigadores, clínicos, docentes y estudiantes avanzados hispanoparlantes.

EL MODELO CATEGORIAL DE ENFERMEDAD LATENTE

La organización y clasificación actual del Manual Diagnóstico y Estadístico de los trastornos mentales de la Asociación Americana de Psiquiatría (APA, 2013) se basa en la descripción de síndromes o conjuntos de síntomas como expresión de una enfermedad latente según el modelo biomédico predominante (Hofmann, 2014). Desde esta perspectiva, por ejemplo, la anhedonia o el insomnio tardío son expresiones de la depresión, así como la tos y la fiebre podrían ser expresiones de alguna enfermedad, como el coronavirus-SARS-2 (COVID-19). Sin embargo, existe una gran diferencia, pues si alguien contrae COVID-19 existe la posibilidad, muy frecuente, de cursar la enfermedad sin síntomas, y solo se determina su presencia a través de un test que comprueba la infección. Por el contrario, en el caso de la depresión no solamente no existe un test biológico que compruebe su presencia o ausencia, lo cual podría

atribuirse, como se hace, a una limitación provisional del estado actual de conocimiento sobre su base neurobiológica, sino que, además, no resulta pensable postular una enfermedad depresiva que se curse sin síntomas. Ni siquiera la categoría de "depresión enmascarada" o "silenciosa" carece de síntomas, sino que sus síntomas están presentes, aunque son más somáticos y menos afectivos. Es decir, si bien puede comprobarse que los síntomas se asocian entre sí con cierta regularidad, la suposición de una entidad latente que explique su agrupamiento resulta poco informativa y no se ha podido respaldar con evidencia sólida, por lo cual queda en un nivel especulativo resultante de trasladar, sin mayores cambios, el modelo biomédico al campo de los trastornos mentales. Es decir, el sistema presenta una gran ventaja a nivel descriptivo, pero al pasar a un nivel explicativo existen controversias que dificultan un consenso.

Además, debe mencionarse el enorme problema clínico que acarrea la frecuente comorbilidad (Cramer, Waldorp, Van Der Maas, y Borsboom, 2010) que, en el campo de los trastornos mentales, resulta ser más la regla que la excepción. Los pacientes presentan un promedio de dos trastornos mentales y, sin cumplir formalmente los criterios para ambos, en la práctica clínica, los pacientes presentan síntomas de otros trastornos. Finalmente, la misma clasificación presenta síntomas que son comunes a dos o más trastornos, lo que da lugar a un solapamiento entre categorías que resulta bastante problemático. Por ejemplo, el insomnio puede ser tanto el síntoma de un trastorno depresivo como de un trastorno de ansiedad generalizada (TAG) o de un trastorno primario del sueño. Estos síntomas son denominados "síntomas puente", como se puede ver en la Figura B.1. Los trece abreviados se organizan del siguiente modo:

Síntomas de Trastorno Depresivo Mayor (TDM). *Tris*: Estado de ánimo deprimido. *Inte*: Disminución importante del interés o el placer. *Suici*: Pensamientos de muerte recurrentes, ideas suicidas recurrentes, intento de suicidio o un plan específico. *Mot*: Agitación o retraso psicomotor. *Culp*: Sentimientos de inutilidad o culpabilidad excesiva o inapropiada. *Pes*: Pérdida importante de peso, sin hacer dieta, o aumento de peso.

Síntomas puente. En este caso, los síntomas puente se refieren a los que comparten las categorías de trastorno depresivo mayor y trastornos de ansiedad generalizada. *Sue*: *Fatig*: Fatigabilidad o falta de energía. *Con*: Alteraciones en la concentración (disminución de la concentración en el TDM, alteraciones en el TAG).

Síntomas de Trastorno de Ansiedad Generalizada (TAG). *Ans*: Ansiedad y preocupación excesiva (anticipación aprehensiva). *Inco*: Incontrolabilidad (al individuo le es difícil controlar la preocupación). *Irri*: Irritabilidad. *Inqu*: Inquietud o sensación de estar atrapado o, como se dice comúnmente en la Argentina, con los nervios de punta. *Mus*: Tensión muscular.

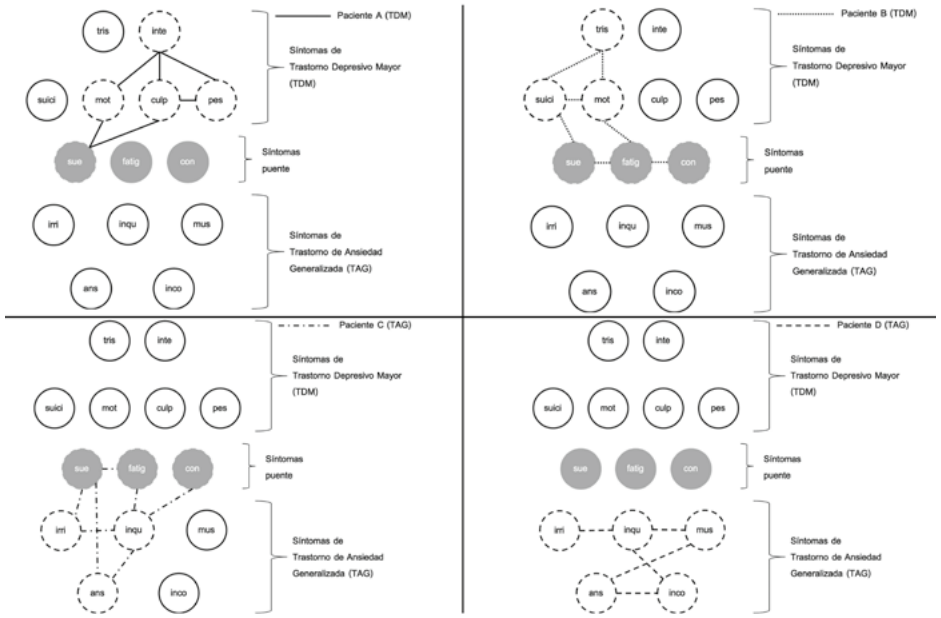

Figura B.1. Ejemplos de redes de síntomas relacionados.

De acuerdo al sistema DSM, puede darse la siguiente situación: dos pacientes, los casos A y B, reciben el diagnóstico de trastorno depresivo mayor (TDM). A pesar de presentar el mismo diagnóstico categorial y ser considerados para las mismas opciones de tratamiento, estos dos pacientes comparten solo un síntoma (alteraciones del sueño). Por su parte, el paciente C recibe el diagnóstico de trastorno de TAG y, al ver los síntomas con independencia de la categoría diagnóstica, puede comprobarse que comparte tres síntomas con el paciente B, con diagnóstico de TDM. Los síntomas que comparten B y C son los síntomas puente: alteraciones del sueño, fatigabilidad o falta de energía y dificultades en la concentración. Es decir que, a pesar de tener diferentes trastornos mentales clasificados por el sistema DSM en diferentes grupos (los trastornos depresivos y los trastornos de ansiedad), los pacientes B y C comparten más síntomas, y probablemente otras características clínicas, que los pacientes A y B, que reciben la misma categoría diagnóstica y, obviamente, son incluidos dentro del mismo grupo de trastornos. Finalmente, el caso D recibe el diagnóstico de TAG y comparte solamente dos síntomas con el caso C, que recibe el mismo diagnóstico (irritabilidad y ansiedad / preocupación excesiva), pero se acerca más al caso B, con diagnóstico de TDM.

Además, la perspectiva biomédica explica el agrupamiento regular de los síntomas, los síndromes, desde un modelo categorial. Desde este enfoque, la categoría diagnóstica no difiere de otra enfermedad médica y subyace como entidad discreta a los síntomas. Los modelos dimensionales se presentaron como una alternativa, por

ejemplo, en el campo de la personalidad (Sánchez, Montes y Somerstein, 2020). Desde un enfoque transdiagnóstico, se enfatiza la importancia de procesos comunes a las diferentes entidades. En los enfoques psicológicos, por ejemplo, la rumiación o el perfeccionismo serían los aspectos comunes a las diferentes entidades. Tanto este enfoque transdiagnóstico como aquel, categorial, ven los síntomas como expresiones de entidades o procesos latentes (Figura B.2). Tanto desde una perspectiva biomédica como desde los enfoques psicológicos transdiagnósticos, existen dos niveles: el superficial o sintomático y el profundo, del cual los síntomas son su expresión ya que allí estarían las causas: los procesos psicológicos o biológicos que serían el problema a resolver.

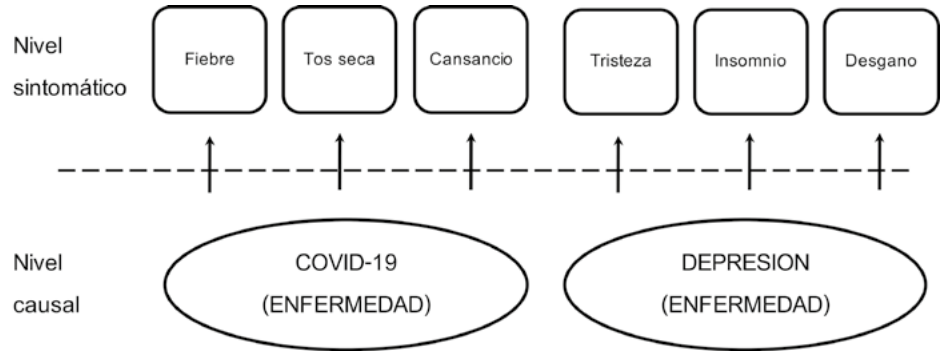

Figura B.2. Modelo biomédico: síntomas como expresión superficial de una enfermedad o trastorno latente.

LAS RELACIONES ENTRE LOS SÍNTOMAS

El modelo de la psicopatología como red de síntomas difiere tanto del modelo categorial como del dimensional al no suponer variables latentes como la causa de la coexistencia de determinados síntomas (Borsboom y Cramer, 2013; Borsboom, 2017; Cramer et al., 2010). Para este enfoque, dicha coexistencia emerge de las interacciones dinámicas y causales que se establecen entre los síntomas. Entonces, los síntomas no son expresiones de una enfermedad, sino que son constitutivos del problema clínico. La hipótesis central de esta perspectiva es la existencia de conexiones causales entre los síntomas. Dichas conexiones son biológicas, psicológicas y sociales. Se trata de complejos mecanismos que, al ser suficientemente fuertes, permiten que la activación de un síntoma lleve a la activación de otros síntomas. Por ejemplo, en una red de síntomas depresivos, el insomnio causa la activación de otro síntoma, como la falta de energía, y luego este activa la irritabilidad; a su vez, la irritabilidad produce deterioro interpersonal y dispara la preocupación, que fortalece el insomnio. Cuando toda la red o sistema de síntomas se activa, se presenta un estado que se automantiene y del cual es difícil salir, es decir, produce un trastorno psicológico o mental.

Esta hipótesis central se aplica a todos los trastornos mentales que pasarían a ser concebidos como estados estables alternativos de redes de síntomas fuertemente conectados (Borsboom, 2017). Por lo tanto, la hipótesis lleva a un modelo explicativo común para todos los trastornos mentales, un "modelo integral de psicopatología" (Ibídem).

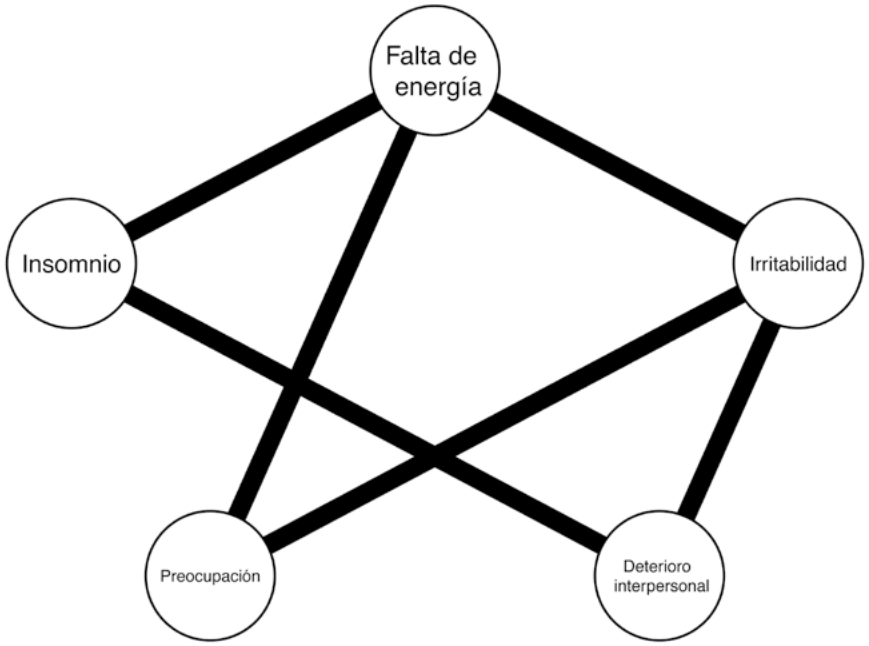

Figura B.3. Red de síntomas depresivos. Las aristas representan asociaciones únicas entre los síntomas, es decir, controladas por la presencia de todos los síntomas en la red. Las asociaciones pueden ser positivas, indicando que la presencia de un nodo aumenta la probabilidad de activación de un nodo vecino, o negativas, donde la ausencia de un nodo aumenta la probabilidad de activación de un nodo vecino.

¿QUÉ ES UNA RED? NODOS Y ARISTAS

La teoría de redes es un campo matemático que estudia las relaciones complejas entre variables y entidades, y se aplica a una amplia variedad de disciplinas, como por ejemplo redes de telecomunicaciones (e. g., Balasundaram y Butenko, 2008), redes de transporte (e. g., Derrible y Kennedy, 2011), redes sociales (e. g., Wrzus et al., 2013) y neurociencia (e. g., Lynall et al., 2010). En general, las redes consisten en nodos que representan la variable o la entidad de interés y aristas que representan la relación entre los nodos.

El enfoque está en la teoría de redes de psicopatología, en la que los nodos representan variables como síntomas de psicopatología y las aristas, las relaciones estimadas entre

estas variables (Borsboom y Cramer, 2013), como demuestra la Figura B.4. Estas relaciones pueden ser positivas o negativas (la activación de un síntoma lleva a la activación / desactivación de otro síntoma), unilaterales o bidireccionales (por ejemplo, la relación entre fatiga y anhedonia puede ser igual en cualquier sentido o la relación de fatiga hacia anhedonia puede ser diferente de la de anhedonia hacia fatiga), y, en general, las relaciones tienen un valor que representa su magnitud (Epskamp y Fried, 2018).

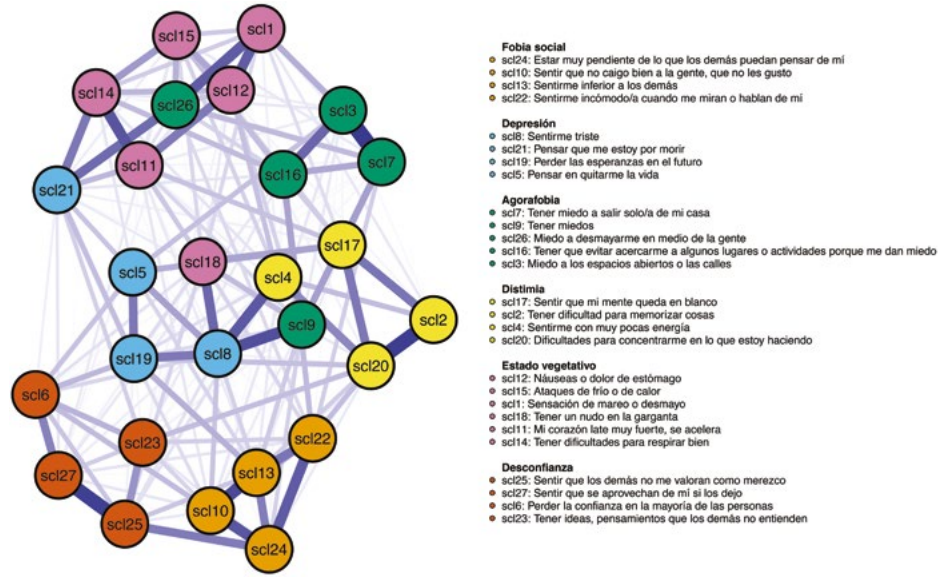

Figura B.4. Una red de psicopatología. Los datos corresponden al estudio Estado de salud mental de la población argentina y variables asociadas 2019 (Etchevers, Garay, Castro Solano y Fernández Liporace, 2019), en el cual se tomó la SCL-27 a una muestra representativa de 1469 habitantes de Argentina. Los nodos representan síntomas del SCL-27 (Symptom Check List, de 27 ítems; Hardt y Gerbershagen, 2001), versión argentina (Castro Solano y Góngora, 2018). Las aristas representan las relaciones estimadas entre los nodos, donde el color azul indica que se trata de una relación positiva, y la amplitud representa magnitud. La SCL-27 mide síntomas de 6 dimensiones, denotados en la leyenda. Se puede observar cómo los síntomas forman racimos entre las dimensiones.

Es importante notar la diferencia entre la teoría y los modelos estadísticos de esta perspectiva de redes (Haslbeck et al., 2021). La teoría propone relaciones causales entre síntomas, en los que la activación de un síntoma de depresión como el insomnio puede causar otro síntoma como la preocupación excesiva. Como, en general, los datos obtenidos sobre los síntomas son observacionales (medidos en una entrevista clínica), los modelos estadísticos no pueden determinar relaciones causales y usan métodos como correlaciones parciales para estimar la varianza única entre variables (Epskamp y Fried, 2018).

DE LAS COMORBILIDADES A LAS REDES COMPLEJAS

Una de las grandes ventajas que ofrece la teoría de redes es explicar el llamado fenómeno de la comorbilidad (Cramer et al., 2010). Dicha comorbilidad supone entidades diagnósticas claras y distintas que se presentan conjuntamente como dos morbilidades diferentes (Bekhuis et al., 2018). Desde la perspectiva de la red causal compleja, los límites entre los trastornos se borran, y ya no se trata de entidades bien diferenciadas, sino de síntomas que se presentan en forma conjunta con cierta regularidad en la medida en que comparten vínculos biopsicosociales que llevan a que unos activen otros y que la red se mantenga (Goekoop y Goekoop, 2014). Es decir, la presencia de ciertos síntomas de modo conjunto no se explica porque sean expresiones de enfermedades latentes como en el modelo biomédico más difundido. Los síntomas no se presentan conjuntamente de modo aleatorio; por el contrario, es más probable que unos síntomas se presenten junto a otros (Hofmann, Curtiss y McNally, 2016). Desde la perspectiva de la red causal compleja, esta presentación regular de los síntomas obedece a los vínculos entre ellos mismos. En lugar de postular una entidad latente, el análisis en red se centra en los síntomas observables, sin tampoco determinar a priori un síntoma cardinal o eje central de la red.

Asimismo, el análisis en red permite revisar conceptos como vulnerabilidad y resiliencia. Una red vulnerable sería aquella en la cual, fácilmente, un síntoma lleva a la activación de otros. Por el contrario, una red resiliente tendría la característica opuesta: si se toma el ejemplo anterior, el insomnio podría producir cansancio, pero no irritabilidad o alteraciones anímicas (Cramer et al., 2016).

LA RELEVANCIA PARA LA PRÁCTICA CLÍNICA

En el ámbito de la psicología clínica resulta particularmente útil considerar las relaciones causales entre los síntomas. En las terapias cognitivo-conductuales, tanto en el análisis funcional de la conducta como en la conceptualización cognitiva del caso, se postulan hipótesis acerca de la relación entre los síntomas del problema clínico y sus consecuencias en la vida de las personas. Estos enfoques ideográficos se articularon de manera discordante con los sistemas de clasificación categoriales en la práctica clínica. Así, un paciente cumple criterios para dos o más trastornos mentales, pero en la práctica, es el psicólogo clínico quien elabora hipótesis acerca de cómo se relacionan dichos trastornos. Por ejemplo, un paciente con un trastorno de ansiedad social y una dependencia del alcohol es visto como un caso en el que la persona ha intentado manejar los síntomas de ansiedad mediante el alcohol, al cual se ha vuelto dependiente. No son dos entidades independientes con enfermedades latentes distintas, sino que están articuladas. Es decir, se trabaja con modelos sintomáticos, algo enfatizado por varios autores, particularmente, en el caso de los síntomas psicóticos, véase Hagen, Turkington, Berge y Gråwe, 2013. A propósito de síntomas psicóticos,

también puede pensarse la relación entre factores cognitivos de mantenimiento de creencias delirantes (Pérez Navarro, 2020).

Como señalan Hofmann, Curtiss y McNally (2015), el modelo de Borsboom y su equipo es particularmente relevante para las terapias cognitivo-conductuales al permitir entender el cambio terapéutico. Hayes, Yasinski, Barnes y Bockting (2015) utilizan la teoría de sistemas dinámicos para estudiar el cambio terapéutico, y se centran en las relaciones entre los síntomas de la depresión a lo largo del proceso terapéutico. Más recientemente, Hofmann, Curtiss y Hayes (2020) propugnan modelos no lineales de cambio psicológico basados en redes complejas que permiten entender relaciones múltiples y bidireccionales entre numerosas variables y avanzan en una dirección similar a la perspectiva de redes causales complejas.

LA RELEVANCIA PARA LA INVESTIGACIÓN

Además de brindar un nuevo marco teórico para la práctica clínica, la perspectiva de la psicopatología como red de síntomas va acompañada de nuevos métodos cuantitativos para la investigación. La mayoría de los métodos disponibles para estimar los modelos se pueden utilizar desde el software libre y gratuito R (R Core Team, 2020). Con base en los datos (por ejemplo, los síntomas presentes / ausentes según un cuestionario clínico), hay diferentes modelos que se pueden estimar. La mayoría de los métodos son exploratorios y estiman las relaciones entre síntomas desde datos observados. Por ejemplo, el Gaussian Graphical Model para datos continuos (Epskamp et al., 2018a) que se puede estimar a través del paquete estadístico R qgraph (Epskamp et al., 2012), o el Ising Model para datos binarios (van Borkulo et al., 2014a) que, a su vez, se puede evaluar al usar el paquete estadístico R IsingFit (van Borkulo et al., 2014b). Con estos datos exploratorios, se pueden visualizar las redes y, en base a las figuras, se pueden generar hipótesis nuevas sobre el desarrollo de síntomas y en qué casos se podría intervenir terapéuticamente (Borsboom y Cramer, 2013). Actualmente, también se desarrolló un método nuevo para estimar modelos confirmatorios de redes confirmativas (Epskamp, 2020).

Una aplicación nueva e interesante sobre la base de la estimación estadística de redes de síntomas es la estimación de modelos ideográficos (Bringmann et al., 2016; Epskamp et al., 2018). Estos modelos intraindividuales se estiman con datos longitudinales, obtenidos, por ejemplo, usando Experience Sampling Method, por los cuales a una persona se le pregunta sobre su estado de ánimo varias veces por día (Epskamp et al., 2018). De esta manera, la investigación puede estudiar procesos individuales dentro de la psicología clínica.

Finalmente, la perspectiva de la psicopatología como red de síntomas brinda nuevas posibilidades para comparar grupos: por ejemplo, si la estructura de una red de

síntomas depresivos (por ejemplo, la magnitud de las aristas) difiere de manera significante entre hombres y mujeres (van Borkulo et al., *in press*).

CONCLUSIONES

Sobre la base del campo matemático de la teoría de las redes, el modelo de red causal compleja aplicado a los problemas de salud mental se caracteriza por centrarse en las interacciones dinámicas y causales que se establecen entre los síntomas, que guían tanto la conceptualización de los trastornos psicológicos como su tratamiento al tender un puente entre las necesidades clínicas y científicas. Los síntomas son constitutivos del problema clínico. Las conexiones causales entre los síntomas son complejas en la medida en que afectan niveles biológicos, psicológicos y/o sociales, ya que la activación de un síntoma lleva a la activación de otros síntomas. Los trastornos mentales son concebidos como estados estables alternativos de redes de síntomas fuertemente conectados y es posible, así, un modelo explicativo, un modelo integral de psicopatología para entender el llamado fenómeno de la comorbilidad, la vulnerabilidad y la resiliencia de otro modo. Además, es coherente con el modelo cognitivo-conductual de los trastornos mentales, que es el que más apoyo empírico posee en la actualidad. En el campo de la investigación, la teoría brinda nuevos métodos formales para estimar y visualizar estas redes, tanto al nivel interindividual, mediante la distribución de síntomas psicopatológicos entre personas en la población general, como al nivel intraindividual, al estimar redes personalizadas. Estos avances tienen implicaciones directas sobre cómo definir el diagnóstico y elegir el tratamiento, y sugiere una agenda certera para futuras investigaciones en psiquiatría, psicología y disciplinas asociadas.

Puede concluirse que la perspectiva de la psicopatología como red causal compleja de síntomas presenta ventajas en varios niveles y puede presentarse como una alternativa al modelo diagnóstico más difundido, el sistema DSM. Este enfoque resuelve el problema de las comorbilidades, el solapamiento entre categorías, la búsqueda de entidades latentes o subyacentes y se acerca más a las perspectivas clínicas en el campo de la psicología, como los modelos cognitivo-conductuales, lo que permite abrir nuevas líneas de investigación que contribuyan a reducir la brecha entre investigadores y clínicos.

C

SUPPLEMENTARY MATERIALS TO CHAPTER 2

C.1 CONSTRUCTING THE FOUR SYMPTOM NETWORKS FOR THE SIMULATIONS

In Chapter 2, we present a proof-of-concept in which we construct four symptom networks that can be placed in the four regimes of the resilience quadrant. Here, we will explain how we constructed the four networks. To make sure that the constructed networks are somewhat bound to empirically estimated parameter values, we first estimate a symptom network from empirical data containing assessments of nine Major Depressive Disorder (MDD) symptoms as our baseline model. Second, we alter the parameters of the baseline model in such a way that the resilience levels of the networks change.

C.1.1 The baseline MDD model

C.1.1.1 Data

The data are collected in the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD; Kendler et al., 1999) and contain binary data on the presence/absence of nine MDD symptoms from 8973 twins from the Mid-Atlantic Twin Registry. The symptoms are: (1) Depressed most of the day, nearly every day, (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day, (3) Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day, (4) Insomnia or hypersomnia nearly every day, (5) Psychomotor agitation or retardation nearly every day, (6) Fatigue or loss of energy nearly every day, (7) Feelings of worthlessness or excessive or inappropriate guilt nearly every day, (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day, and (9) Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. Symptoms were measured during a psychiatric interview using an adaptation of the Structured Clinical Interview for DSM-III-R (Spitzer et al., 1992).

C.1.1.2 Model

We estimate the symptom network model using the Ising model (Ising, 1925). The Ising model is a relatively simple model which has been frequently applied to mental health and specifically depression for its ability to show complex behavior in line with the development of psychiatric disorders (Ising, 1925; see van Borkulo et al., 2014, Marsman et al., 2018 and Finneman et al., 2021 for an extensive description of the Ising model used in psychology). Symptoms are encoded as either “present” (1) or “absent” (0). The Ising model is symmetric, meaning that the relationships between the nodes are undirected; e.g., the relationship from “insomnia” to “depressed mood” is the same as the relationship from “depressed mood” to “insomnia”. The connections between symptoms are called *edge weights* and are estimated with logistic regression

analyses. The internal dispositions of symptoms are called *threshold parameters*, which are calculated as the intercept of the logistic regression equation (van Borkulo et al., 2014).

C.1.2 Alter the parameters of the baseline model

To construct the *resilient network*, we decrease the edge weight parameters of the baseline MDD model by multiplying the baseline edge weights with 0.8, and increase the threshold parameters by multiplying the baseline thresholds with 1.2. For the *remitting network*, we multiply the parameters in the opposite direction but with smaller values, in order increase the instability of the network's dynamics. We multiply the edge weights of the baseline model with 1.1 and the threshold parameters of the baseline model with 0.95. For the *relapsing network*, we multiply the edge weights of the baseline model with 1.1 and the thresholds with 0.9. To construct the *chronically depressed network*, we increase the connectivity of the depressed model by multiplying the edge weights of the baseline model with 1.2 and decrease the threshold parameters (i.e., making the preference for absence weaker) by multiplying the baseline thresholds with 0.8. In the simulations with the Glauber dynamics (see Supplementary Section: C.2.1. Simulating observations without perturbations) we set the beta parameter to 1.5 instead of the usual setting of 1. This leads to a stronger effect from the parameters and more stable simulations.

C.2 SIMULATING THE PROJECTED AND PERTURBED OBSERVATIONS

In this section, we explain the techniques used to simulate the projected observations and perturbed observations for the four Ising network models as described in Chapter 2.

C.2.1 Simulating observations without perturbations

The symptom development patterns of the Ising model will always strive to be in the configuration of symptoms that costs less *energy* (Dalege et al., 2019). The energy for every possible configuration of symptoms (i.e., all combinations of absent and present symptoms) depends on the threshold parameters and the edge weight parameters. The energy for every symptom combination in the Ising model is calculated with the Hamiltonian in Formula 1.

$$H(X) = -\sum_{i} \tau_i X_i - \sum_{<i,j>} W_{i,j} X_i X_j \quad (1)$$

Formula 1 gives the Hamiltonian energy for two symptoms i and j, but can be extended for networks with more symptoms. The energy for the configuration X of the network (for example, both symptoms are present) is calculated from the threshold τ_i of symptom i, the edge weights $W_{i,j}$ between symptom i and its neighboring symptom j, and the current presence or absence $X_i X_j$ of both symptoms.

C.2.2 Simulating observations with perturbations

Ising model dynamics can be simulated using an algorithm called Glauber dynamics (Glauber, 1963). Glauber dynamics are an established method for simulating dynamics from an Ising model (e.g., see Levin et al., 2008). The idea behind the method is that for every simulated observation only one symptom can change its state from presence to absence or vice versa, in order to mimic a continuous process of development. The algorithm selects one random symptom for every novel simulated observation. The state of the symptom is then flipped, meaning that if the symptom was currently present it gets deactivated (denoted by changing the state of the symptom from a 1 → 0) and vice versa[12]. The difference between the current state and the flipped state of the symptom is calculated by computing the energy difference between the two situations (see Formula 1). The energy difference between the current and flipped state of the symptom determines the probability that the symptom either changes its state or remains in the current state; the lower the energy of the alternative state, the higher the probability the symptom's state will change. A stochastic process is added to the simulation by adding a transition probability. In our simulations we simulate 10.000 observations for every network, to ensure the stability of our results.

To simulate the alleviating and aggravating interventions as described in the manuscript, we perturb the simulations every 1000th observation (see Figure 2.4 in the chapter). Thus, perturbations are administered 10 times. We stop the Glauber dynamics algorithm every 1000th observation, and force all symptoms to be present or absent, depending on whether we are simulating an alleviating or aggravating intervention. Afterwards, the algorithm continues in its ordinary fashion, calculating which symptom configuration is most likely for every observation. Depending on the parameters for every network model, the symptoms 'recover' from this intervention, or they maintain stuck in a situation with high or low symptom activation.

12 Following the suggestions as made in Haslbeck, Epskamp, Marsman & Waldorp (2018), we use the transformed {0,1} parameters of the Ising model (instead of the {-1,1} parameters) to compute the Glauber dynamics with networks that are estimated from {0,1} binary data.

D

SUPPLEMENTARY MATERIALS TO CHAPTER 3

D.1 SUPPLEMENTARY TABLE

Table D.1. SCL-27 variable names

Variable label	Variable description
SCL-1	Feeling very self-conscious with others
SCL-2	Feeling blue
SCL-3	Feeling afraid to go out of your house alone
SCL-4	Feeling fearful
SCL-5	Thoughts of death or dying
SCL-6	Your mind going blank
SCL-7	Trouble remembering things
SCL-8	Feeling that people are unfriendly or dislike you
SCL-9	Feeling low in energy or slowed down
SCL-10	Nausea or upset stomach
SCL-11	Hot or cold spells
SCL-12	Others not giving you proper credit for your achievements
SCL-13	Faintness or dizziness
SCL-14	Feeling that people will take advances of you if you let them
SCL-15	Feeling hopeless about the future
SCL-16	A lump in your throat
SCL-17	Feeling that most people cannot be trusted
SCL-18	Heart pounding or racing
SCL-19	Having ideas or beliefs that others do not share
SCL-20	Feeling afraid you will faint in public
SCL-21	Feeling inferior to others
SCL-22	Thoughts of ending your life
SCL-23	Feeling uneasy when people are watching or talking about you
SCL-24	Trouble concentrating
SCL-25	Having to avoid certain things, places or activities that frighten you
SCL-26	Trouble getting your breath
SCL-27	Feeling afraid in open spaces or on the streets

D.2 SUPPLEMENTARY FIGURE

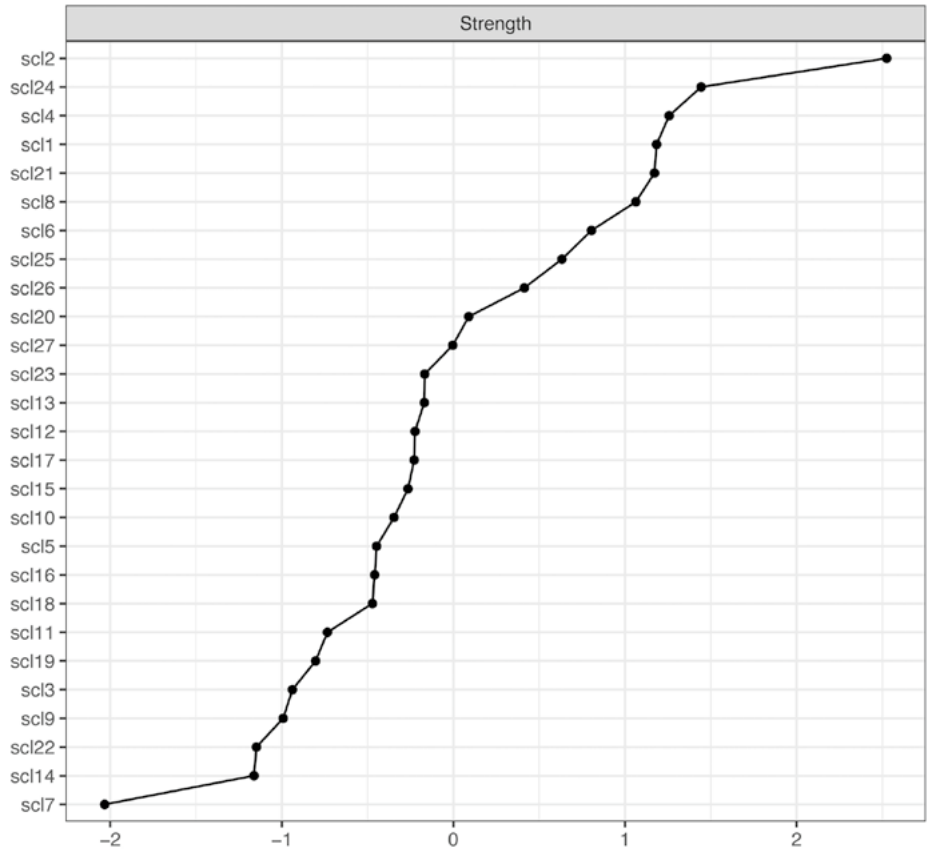

Figure D.1. ***Centrality plot showing node strength of SCL-27 nodes.*** The x-axis shows node strength on standardized z-scores, the y-axis shows all SCL-27 variables. The upper variables have highest node strength, and the lower variables have lowest node strength.

E

SUPPLEMENTARY MATERIALS TO CHAPTER 5

E.1 INSPECTING MEASUREMENT OCCASIONS

One of the assumptions of the multilevel VAR model is equal time intervals between measurement occasions. The full version of the daily surveys, which contained assessments of mood and depression complaints, were sent out on the first three days and afterward on two randomly selected days of the week, therewith violating the assumption of equal time intervals between measurement occasions. Inspecting the response rate of the full survey over the study period showed a clear three-day interval pattern; see the upper panel of Figure E.1. In addition, we see an apparent occurrence of peaks within these three-day intervals. Therefore, we decided to group days into measurement occasions defined by a three-day window. This insured data at every measurement occasion; see the lower panel of Figure E.1.

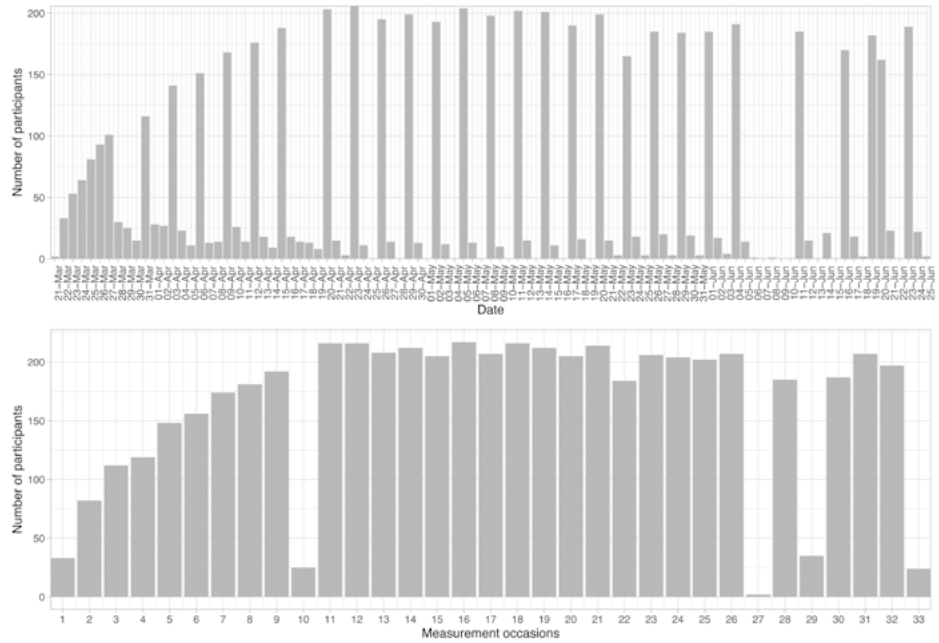

Figure E.1. The response rate for the full survey over the study period from March 20th, 2020 until June 26th, 2020. Inspecting the number of participants who completed assessments compared to the number of participants who completed measurement occasions, we found no significant loss of participants, see Figure E.2. In line with recommendations for the multilevel VAR model, we selected participants with at least twenty measurement occasions (Jordan, Winer & Salem, 2020).

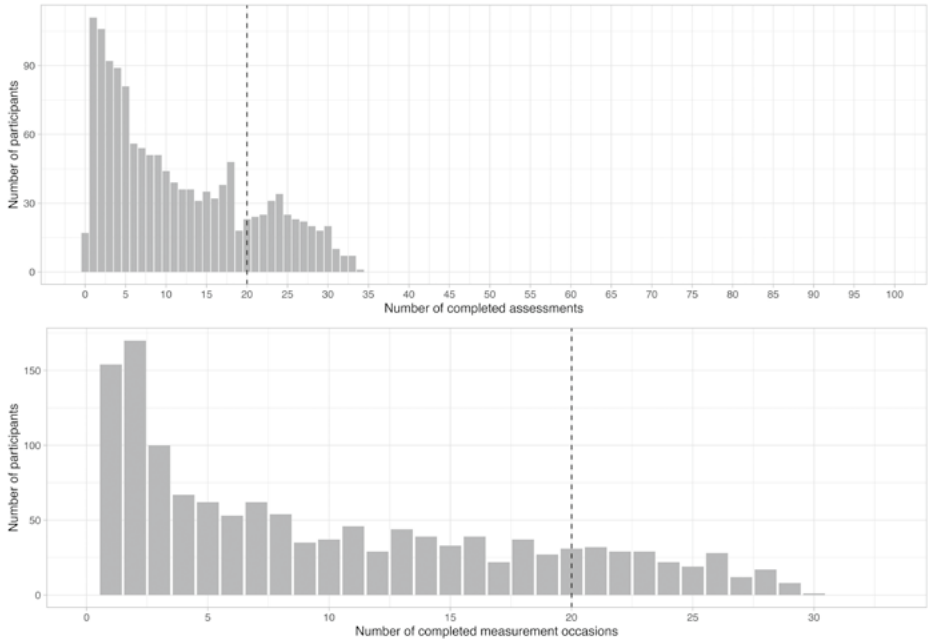

Figure E.2. Number of participants and measurement occasions. The upper panel shows the number of participants completed assessments. The lower panel shows the number of participants and the number of completed measurement occasions. The dotted line represents the cut-off value of 20 measurement occasions recommended to estimate a *MLVAR* network model.

E.2 SAMPLE CHARACTARISTICS

Table E.1. **Demographic characteristics of final sample (n=228)**

Characteristics	**Mean**	**SD**
Age	44.8	19.2
	N	Percentage
Gender		
Female	186	81.6%
Male	42	18.4%
Race/ethnicity		
African-American	1	0.4%
Asian	21	9.2%
White	207	90.8%
Hispanic/Latinx	5	2.2%
More than one race	4	1.8%
Cultural Background		
North-America	206	90.4%
South-America	2	0.9%
Africa	1	0.4%
Asia	4	1.8%
Europe	10	4.4%
Oceania	5	2.2%
Annual household income		
$0-$25,000	21	9.2%
$25,001-$50,000	36	15.8%
$50,001-$75,000	42	18.4%
$75,001-$100,000	40	17.5%
$100,001-$150,000	32	14%
$150,001-$250,000	31	13.6%
$250,000+	26	11.4%
Education		
High School Diploma	5	2.2%
Some college	19	8.3%
College degree	56	24.6%
Some post-bacc education	29	12.7%
Graduate, medical or professional degree	119	52.2%

***Table E.2*. Mean and standard deviation for PHQ-9, PA, and NA variables at baseline for the final sample.**

	Mean	SD
Selected sample (*n*=228)		
PHQ9	5.90	4.14
Inspired	2.07	1.03
Alert	2.95	1.07
Excited	1.8	0.88
Enthusiastic	2.04	1.03
Determined	2.61	1.15
Afraid	1.84	1
Upset	1.67	0.86
Nervous	2.12	1.02
Scared	1.97	0.97
Distressed	1.92	0.89

E.3 CLUSTERING ANALYSIS

Based on original results, a distinct separation between the different network components (i.e., positive affect (PA), negative affect (NA), and depressive complaints) seemed less evident in the temporal network compared to the contemporaneous and between-persons network. Relatively more edges between components than within components were present within the temporal network. In order to vindicate these results, post-hoc clustering analyses were performed using two different algorithms: *Spinglass* and *Walktrap*. In addition, a sensitivity analysis was performed for both clustering techniques, i.e., the algorithm was repeated hundred times to ensure a median number of clusters.

The Spinglass algorithm cannot account for nodes not connected to any of the other nodes within the network. As the node "PsychMot" is disconnected from any of the remaining nodes in the network, it cannot be considered. Sensitivity analysis for Spinglass suggested, in line with the original network components, a median of 3 clusters for the contemporaneous network as well as for the between-persons network, see the two right panels of Figure E.3. For the temporal network, a median of 5 clusters was detected; see the left panel of Figure E.3. Suggested cluster membership for each node differed per iteration, therefore the group membership as depicted in *Figure 3* should be taken as exemplary. Results for the Walkrap algorithm were in line with results from Spinglass for the contemporaneous and between-persons network; a median of 3 clusters was found, see the two right panels of Figure E.4. For the temporal network, a median of 4 clusters was detected; see the left panel of Figure E.4. Node cluster membership was consistent, however, detected clusters consisted of PA, a combination of PA, NA, and depression complaints, or depression complaints.

Interestingly, both clustering techniques confirmed the original three components (i.e., PA, NA, and depression complaints) in the contemporaneous network and the between-person network. However, these components were not confirmed for the temporal network. In addition, node cluster membership for the temporal network, as indicated by Spingglass, was highly unstable, and clusters consisted of a mixture of nodes from multiple components using Walktrap, corroborating the notion that from one measurement occasion upon the next, there is a more direct interplay between affect and depression, while, within a given time frame, or on average, there is a clearer demarcation between PA, NA, and depressive complaints.

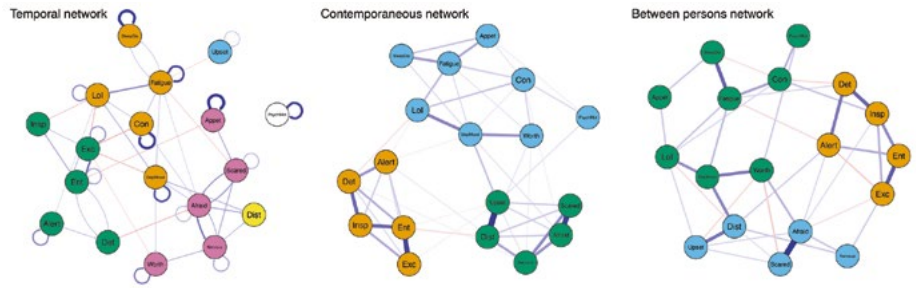

Figure E.3. Results for clustering analysis with Spinglass algorithm. The left panel displays the average fixed-effects temporal network model, portraying relations from one measurement occasion onto the next. The middle panel displays the average fixed-effects contemporaneous network model, portraying effects that play a role in the same measurement occasion after controlling for the temporal effects. The right panel displays the between-persons network model is displayed, indicating effects between persons (i.e., the interindividual differences). Blue edges indicate positive relations, whereas red edges indicate negative relations. Nodes are colored according to the suggested cluster. Spinglass cannot account for nodes that are not attached to the network. Therefore, the node "PsychMot' is not colored; it does not belong to any cluster. A median of 5 clusters was detected for the temporal network. However, sensitivity analyses found that the suggested membership for each note differed for the temporal network; therefore, the colors depicted here should be considered exemplary. For the contemporaneous network, a median of 3 clusters was detected as well as for the between-persons network. For a legend of node names, see Table E.3.

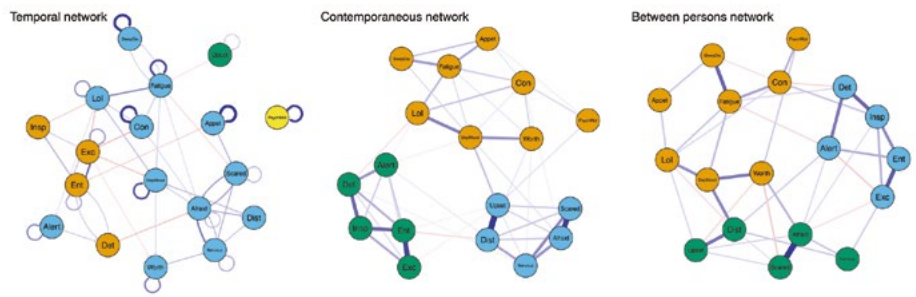

Figure E.4. Results for clustering analysis with Walktrap algorithm. The left panel displays the average fixed-effects temporal network model, portraying relations from one measurement occasion onto the next. The middle panel displays the average fixed-effects contemporaneous network model, portraying effects that play a role in the same measurement occasion after controlling for the temporal effects. The right panel displays the between-persons network model is displayed, indicating effects between persons (i.e., the interindividual differences). Blue edges indicate positive relations, whereas red edges indicate negative relations. Nodes are colored according to their suggested cluster. A median of 4 clusters was detected for the temporal network. For the contemporaneous network, a median of 3 clusters was detected as well as for the between-persons network. For a legend of node names, see Table E.2.

***Table E.3.* Legend of node names.**

Node names
Insp: Inspired
Alt: Alert
Exc: Excited
Ent: Enthusiastic
Det: Determined
Afr: Afraid
Ups: Upset
Ner: Nervous
Scar: Scared
LoI: Loss of Interested
DepMood: Depressed Mood
SleepDis: Sleep disturbances
Fatigue: Fatigue
Appet: Loss of appetite
Worth: Feelings of Worthlessness
Con: Concentration problems
PsychMot: Psychomotor agitation or retardation

E.4 SENSITIVITY CHECKS

We observed a strong correlation between the maximum absolute change in PHQ-9 score and the temporal network density (r = 0.77). Interestingly, when splitting the change in PHQ-9 score into alleviation or aggravation, we saw that this pattern is present in both directions: a larger change in PHQ-9 score is associated with a more strongly connected temporal network. In order to inspect the robustness of our findings, we conducted two sensitivity checks.

E.4.1 Detrending

As a first sensitivity check, we inspected whether trends in the data influence the observed correlation. To investigate this, we first tested for trends in the data using *kpss.test()* in *R*. Next, we detrended individual data by fitting linear regression models on each variable, regressing out a linear trend on measurement occasion, at an alpha of 0.05. Afterward, we estimated the multilevel VAR model on the detrended data. We computed density measures for each individual's network and correlated this with their absolute maximum change in PHQ-9 scores. Results indicated a slightly stronger correlation (r = 0.79) between temporal network density and absolute maximum

change in PHQ-9 score, see Figure E.5. We, therefore, conclude trends in the data do not affect the main conclusions made in the chapter.

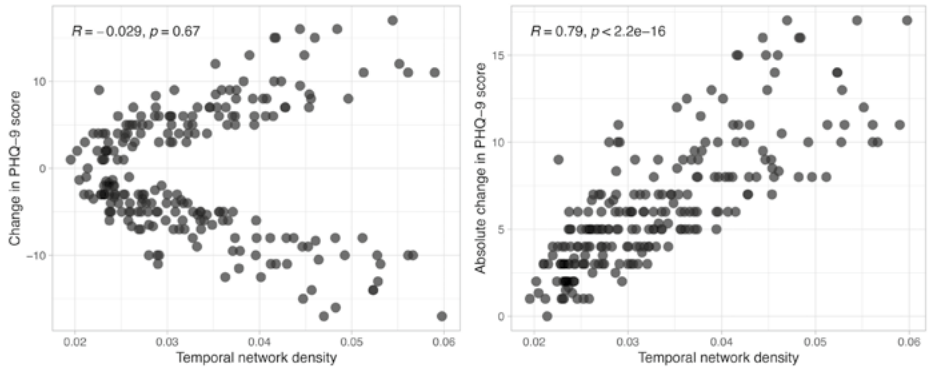

Figure E.5. Correlation between individual temporal network density and the (absolute) maximum change in PHQ-9 score after detrending the data.

E.4.2 Network density for affect items and PHQ-9 change score

As a second sensitivity check, we investigated the possibility that the correlation was driven by the fact that the network includes the PHQ-9 items such that the temporal density is, at least in part, based on the same information (i.e., PHQ-9 items) that is also used to relate the density to (i.e., the absolute maximum change in PHQ-9 total score). Therefore, we investigated the relation between network density and maximum change in PHQ-9 score when including only the affect states into the networks.

We re-estimated mlVAR networks including only positive and negative affect items. Based on these networks, we re-calculated the network density for each individual (i.e., the average absolute strength of their temporal associations). We correlated this network density with the absolute maximum change in PHQ-9 total score. As can be expected, removing the PHQ-9 items from the network decreased the strength of the observed correlation. However, we still clearly observed a positive association between the network density and the absolute change in PHQ-9 score (r = 0.4), see Figure E.6.

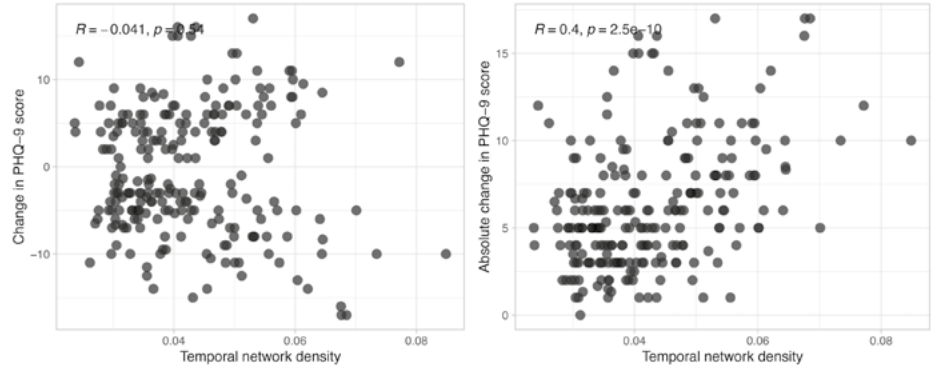

Figure E.6. Correlation between individual temporal network density including only positive and negative affect and the (absolute) maximum change in PHQ-9 score.

F

SUPPLEMENTARY MATERIALS TO CHAPTER 6

F.1 SENSITIVITY ANALYSES WITH SMALLER INTERVENTIONS

We conducted a sensitivity analysis to study how NIRA results change when interventions are represented by altering the threshold parameters with one standard deviation from the thresholds' distribution - instead of two standard deviations.

Results indicate that the projected effects from NIRA are smaller compared to the results reported in our study, as can be expected from the weaker intervention. However, the projected effects from NIRA still differ over the distinct nodes. Potential propelling effects diminish, as node-specific interventions decrease the network's sum score with a maximum of one. In other words, the symptom-specific intervention is projected to deactivate the targeted symptom, but no neighboring symptoms.

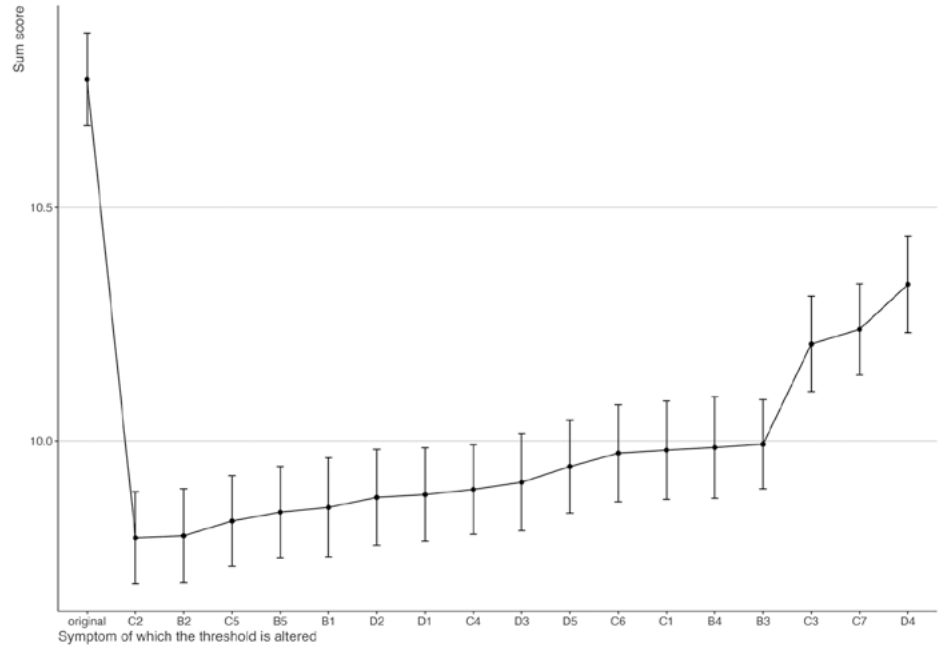

Figure F.1. Projected effects from alleviating NIRA interventions when interventions are weaker than the ones reported in the main study.

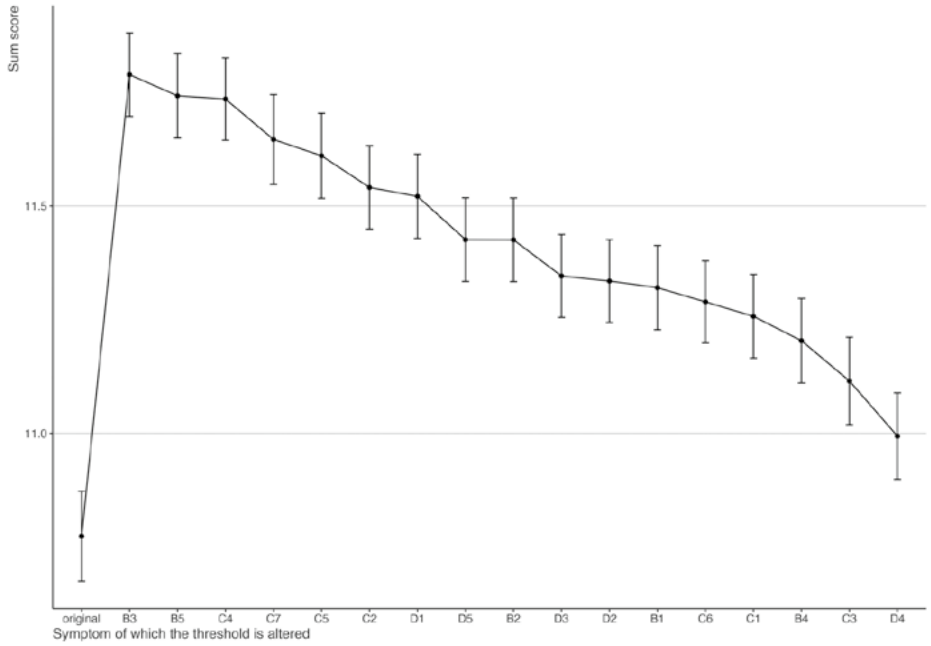

Figure F.2. Projected effects from aggravating NIRA interventions when interventions are weaker than the ones reported in the main study.

F.2 STABILITY ANALYSES OF NIRA USING BOOTSTRAPPING

We tested the stability of NIRA outcomes using bootstrapping (Epskamp et al., 2018). The test is conducted using the same principles as the algorithm itself, however, as a starting point, a sample size of 100.000 observations is used. The input network for this test remains the PTSD network used in the empirical illustration of Chapter 6. The steps of the algorithm previously described in section 6.2.1 are followed (except for the increased sample size) until the sum score distributions are yielded. The test stores the 11 distributions of 100.000 sum scores and now selects 90.000 observations from the original 100.000. For this sample size the sum score distributions are also stored, and the average Pearson correlation between these sum score distribution and the sum score distribution of 100.000 observations is computed. These steps are repeated with sample sizes of 80.000, 70.000, 60.000, 50.000, 40.000, 30.000, 20.000, 10.000, 5000, 1000 and 500. In every step, more cases are dropped from the original 100.000 observations. Therefore, the test technique can best be described as a case dropping bootstrap, which was inspired by the *bootnet* R package (Epskamp et al., 2019), in which a similar technique is presented.

Figure F.3 shows the test results. Each point represents the average Pearson correlation between the sum score distributions of 100.000 observations and the sum score

distributions of the corresponding number of observations shown on the x-axis. The grey area surrounding the points represents the 95% confidence interval given the correlation and the relevant sample size. From this figure a drop can be seen in the correlations with a cut-point after the sample sizes under 5000. On the other hand, all computed correlations are above 0.97, which is extremely high. To be on the safe side, we use the algorithm with a default sample size of 5000. However, even with smaller sample sizes, the algorithm has proven to be a reliable and stable method.

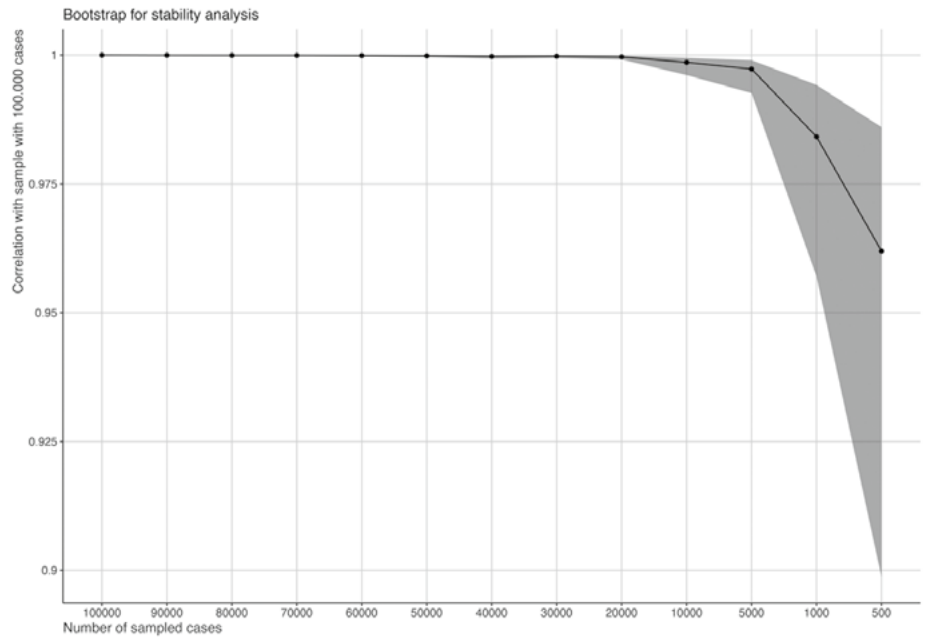

Figure F.3. Stability Analyses of the NIRA using Bootstrapping.

F.3 ISING MODEL DYNAMICS

For a complete overview of the dynamics of the Ising model, we refer to the papers by Haslbeck et al., (2020) and van Borkulo et al. (2014). Here follows an explanation similar to the one in chapter 4.

Symptom activation patterns follow from the probability distribution of the Ising model. The Ising model for two nodes (X_1, X_2) is given by formula (1), which extends to n nodes (Haslbeck, Epskamp, Marsman, & Waldorp, 2020):

$$P(X_1, X_2) = \frac{1}{Z}\exp\{\tau_1 X_1 + \tau_2 X_2 + W_{12} X_1 X_2\} \quad (1)$$

In this formula, X_1 and X_2 are elements of {0,1}, $P(X_1, X_2)$ is the probability that the two nodes are in a specific state (X_1, X_2), τ_1 denotes the threshold of the node X_1, and W_{12} denotes the edge weights of the neighboring nodes X_1 and X_2. Z is a normalizing constant that denotes the sum of the potentials of all possible states.

G

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SUMMARY

Mental disorders place a huge burden on the person suffering, such as having a lower quality of life, but also on their environment and society at large. Often, mental disorders arise after facing stressful and adverse events, such as the death of a loved one, physical illness, or poverty. However, this is not always the case. For example, many people experience at least one potentially traumatizing event in their life (such as 90 % of people in Western countries), but only 8% of the population is diagnosed with Post-Traumatic Stress Disorder. Although many people develop some mental health problems directly after facing adversity, these problems often disappear relatively rapidly. In other words, most people 'bounce back' towards good mental health. This capacity to maintain or relatively quickly return to normal psychological functioning after suffering from adversity is called *resilience*.

Because resilience is always defined in relation to some negative event, it is difficult to study the concept scientifically. The obvious reason for this is of an ethical nature: we cannot expose participants to potentially traumatic events for the sake of science. But even if we can come up with smart workarounds in our scientific design, resilience has proven to be a complicated concept to investigate. Resilience is not a static concept, meaning that one could be resilient against one type of adversity (e.g., losing one's job), but not against another negative event (e.g., losing one's parent). Additionally, resilience levels change over time: one may be resilient at one point in life but not in another. These fluctuations in resilience are associated with different *protective factors* and *risk factors*, which help or hinder a person in maintaining good mental health. Examples of protective factors are having a positive outlook on life, a good financial basis, and a big social support system. On the contrary, risk factors such as a neurotic personality or having suffered from a difficult childhood are likely to indicate a vulnerability for the development of mental disorders. Now, these risk and protective factors do not operate in isolation but also interact among themselves. For example, having suffered from childhood abuse can make it more difficult to maintain healthy relationships with romantic partners, which, in turn, can lead to other problems. How can we investigate these complex interactions between protective factors, risk factors, and resilience?

An example of how resilience can be viewed as a result of complex interactions comes from the research of ecosystems. Ecosystems are represented as *complex systems* containing various interacting elements that can end up in self-sustaining states. A good example of such an ecosystem is a lake. A lake contains elements such as fish, nutrients and algae, which all depend on each other. The lake can be clear, representing a situation in which all the elements thrive and maintain a healthy balance of vegetation, fish population and nutrients. However, this healthy balance can be disturbed, for example, if the algae in the lake start growing. This increased number of algae can limit the light that reaches the bottom of the lake, reducing the vegetation that can grow there. In turn, this decrease in vegetation confines the fish population

and nutrients, and, as such, leads the lake to have turbid water. This causal chain of disruption is not easily reversed, which is why the turbid water situation is understood as a self-sustaining state. An ecosystem, such as the lake, can be implemented in a computational model and studied under different conditions and *perturbations* (i.e., stressors or disruptions) using simulations, which is called *simulation modeling*. This approach has been extended over the past decades, for example, to understand the effects of the climate crisis on specific ecosystems like rainforests. By generating testable hypotheses from the model, one can observe the accuracy of predictions and improve models and theories.

Taking this approach to psychology opens exciting possibilities for the study of resilience. In this dissertation, I combined existing complexity models of mental health with simulation modeling to develop a novel framework for the investigation of psychological resilience. The existing complexity models originate in the *network theory of psychopathology*, which proposes that mental disorders act as complex systems organized in a network of interconnected symptoms. These symptom networks can be located in a healthy state, meaning that most symptoms are currently absent, or evolve towards a disorder state, in which many symptoms are activated. By studying the dynamics of these networks and adding simulated *clinical interventions* – which pull the network towards a healthy state – or *stressful perturbations* – pulling the network towards a disorder state, we can investigate how the symptom network may behave under different conditions. As such, we can assess the resilience of these symptom networks – according to their model.

The proposed approach provides an alternative to the ethical and methodological challenges to study resilience that were mentioned before. Instead of having to expose people to real adversity, we can use models representing people's mental health and perturb these models using simulations. Additionally, these complexity models conceptualize the interrelations between all relevant factors instead of representing resilience as one outcome variable. Thus, in the proposed framework, resilience is not an entity within the network (such as a variable that could be isolated), but a *property* of the network.

However, the existing symptom networks need to be expanded on several aspects to accommodate a framework that incorporates findings from the resilience research literature. The chapters in this dissertation all discuss one of these issues.

Chapter 2 shows how we can assess the resilience of symptom networks using simulations. Complex systems produce their own patterns of behavior, depending on how the elements of the system are interrelated. Thus, to understand the behavior of a complex system, we need to understand the system's constitution (i.e., which nodes in the network are connected to each other, and how easily will these nodes

be activated?). The chapter shows how the *architecture* of symptom networks relates to their resilience against perturbations. A network's architecture consists of the *edge weights* between the symptoms, which represent the strength of the connections, and the *thresholds* of every symptom, which represents their disposition for activation. Resilient networks are generally characterized by high symptom thresholds and weak connections between the symptoms. However, different combinations of node and edge parameters can lead to the same resilience level indicating various pathways in which a network's resilience could be improved. Notably, the differences in parameter values that result in different resilience levels are slight. This potentially explains why resilience is thought to be dependent on complex configurations of factors that support resilience. These findings are presented by introducing the *resilience quadrant* that organizes symptom networks based on their most likely *state* (healthy or disordered) and *stability* against perturbations (stable or unstable). A resilient network is located in a stable and healthy state.

Chapter 3 moves from network models of *mental disorders* towards models of *mental health*, by expanding symptom networks with external risk and protective factors. The chapter presents a formal, complex system of mental health that can accommodate the factors that are often related with the development of resilience in the research literature. Essentially, the chapter proposes that these external factors may alter specific parameters of the symptom network, and as such, make the network more vulnerable or more resilient against perturbations. The chapter presents several simulation studies that show what this process may look like. As such, resilience can be represented from a multifactorial perspective in which risk and protective factors are interconnected and affect the presence and stability of symptoms.

Chapter 4 expands the complexity model of mental health with *slow* and *fast* processes. This is because the different risk and protective factors that influence resilience most likely operate on different timescales. An example of a slow process that could affect mental health is personality. People's personality can change, but this happens over the span of a lifetime. It is unlikely that you will score very differently on a personality test from one year to another, but more differences are expected when comparing test results from when you're 20 years old and when you're 70 years old. In the proposed network model of mental health, personality factors (the slow process) alter the architecture of the psychopathology network (the fast process) in a non-trivial way. We apply the model to the examples of neuroticism (the slow process) and depression (the fast process). The applied model connects empirically informed depression and neuroticism networks and shows that simulations from the theoretical model result in plausible empirical patterns representing essential phenomena. This chapter was implemented in an online simulation tool to make the presented study easy to understand and replicate.

Chapter 5 investigates how risk and protective factors may interact with the evolution of depressive complaints within and across individuals over longer periods of time. The study in this chapter focuses on the interplay between fluctuations in positive and negative affect, and the course of depressive complaints. We analyzed data from 228 participants who completed at least 20 assessments spanning between 9-14 weeks. We estimated longitudinal networks including positive affect, negative affect, and depressive complaints. After inspecting these individual networks, we found that people who were represented by *denser* networks (more and stronger connections between the variables), showed either an alleviation or aggravation of depression complaints over time. This means that the density of network models could indicate the fluctuations of the variables over time, when zooming in on individual trajectories.

Chapter 6 presents a novel method and corresponding R-package (*nodeIdentifyR*) to study the projected effects of symptom-specific interventions in symptom networks. The effect of a symptom-specific intervention is computed by considering the behavior of the whole network. The method can be applied to empirically estimated symptom networks to identify which specific symptoms would be the optimal targets for therapeutic interventions. Additionally, the method can study which symptom-specific stressful perturbation would have the most unfavorable effect on the network. This could provide information on the vulnerabilities in the network that may have to be considered for preventive care. By taking a complexity approach in which the effects from targeted interventions are studied on the behavior of the whole network, the method anticipates propelling effects that are difficult to identify without simulations.

Finally, Chapter 7 provides the general discussion of the dissertation with an overview of the challenges that lay ahead to further advance the proposed framework. For example, developing novel complexity (network) models that can vary over time to better understand how people develop resilience. Additionally, future research could focus more on the protective mechanisms that improve someone's resilience. Although this dissertation has opened up the symptom networks to include positive mental health variables from a methodological and conceptual aspect, it did not study protective mechanisms from a substantive point of view. Future research may use the proposed framework to broaden our focus from symptom development towards the development of protective factors and resilience mechanisms. Furthermore, more research is needed to apply the proposed framework to intra-individual processes, such that we could assess the resilience of an individual network. Lastly, the next step to further develop this framework is the empirical validation of both complexity models, specifically, the network models, as the simulated dynamics as proposed in this dissertation. In this chapter, I give an overview of different options to start such validations.

As such, this dissertation developed a framework to investigate psychological resilience from a complex systems perspective using simulations. The framework opens novel possibilities for assessing the resilience of symptom networks and shows different possibilities for the expansion of these models to accommodate behavior from the resilience research literature. However, the framework could also be used in a broader sense in different fields, such as larger behavioral transitions outside of the mental health context. A modeling approach that studies different scenarios can help to understand how different interventions may play out, as these cannot be understood in isolation. One could investigate how long-term, stable behavioral transitions in society (e.g., the sustainable energy transition) could be achieved using the proposed framework. Thus, investigating resilience as a property of complex systems through simulations could open up many novel and exciting research programs.

I

NEDERLANDSE SAMENVATTING

Psychologische stoornissen brengen een enorme belasting voor de persoon die eraan lijdt met zich mee, zoals een lagere levenskwaliteit, maar zijn ook belastend voor de naaste omgeving en de samenleving in het algemeen. Vaak ontstaan psychische stoornissen na stressvolle en moeilijke gebeurtenissen, zoals de dood van een dierbare, ziekte of financiële problemen. Dit is echter niet altijd het geval. Veel mensen maken bijvoorbeeld ten minste één potentieel traumatiserende gebeurtenis in hun leven mee (zoals 90% van de mensen in Westerse landen), maar bij slechts 8% van de bevolking wordt een posttraumatische stressstoornis vastgesteld. Hoewel veel mensen direct na een tegenslag geestelijke gezondheidsproblemen ontwikkelen, verdwijnen deze problemen vaak betrekkelijk snel. Met andere woorden, de meeste mensen "stuiteren terug" naar een goede geestelijke gezondheid. Dit vermogen om te blijven functioneren of relatief snel terug te keren naar normaal psychisch functioneren na tegenslag wordt *veerkracht* genoemd.

Omdat veerkracht altijd wordt gedefinieerd in relatie tot een negatieve gebeurtenis, is het moeilijk om het concept wetenschappelijk te bestuderen. De voor de hand liggende reden hiervoor is van ethische aard: we kunnen deelnemers niet blootstellen aan potentieel traumatische gebeurtenissen omwille van de wetenschap. Maar zelfs als we slimme omwegen kunnen bedenken in onze wetenschappelijke opzet, blijkt veerkracht een ingewikkeld concept om te onderzoeken. Veerkracht is geen vaststaand concept, wat betekent dat iemand veerkrachtig kan zijn tegen één soort tegenslag (bijvoorbeeld het verliezen van zijn baan), maar niet tegen een andere negatieve gebeurtenis (bijvoorbeeld het verliezen van een ouder). Bovendien verandert het niveau van veerkracht in de loop van de tijd: iemand kan op een bepaald moment in haar leven veerkrachtig zijn, maar op een ander moment juist niet. Deze schommelingen in veerkracht hangen samen met verschillende *beschermende factoren* en *risicofactoren*, die iemand helpen of juist hinderen bij het behouden van een goede geestelijke gezondheid. Voorbeelden van beschermende factoren zijn het hebben van een positieve kijk op het leven, een goede financiële basis, en een groot sociaal supportsysteem. Risicofactoren zoals een neurotische persoonlijkheid of een moeilijke jeugd wijzen daarentegen op een kwetsbaarheid voor de ontwikkeling van psychische stoornissen. Deze risicofactoren en beschermende factoren staan niet op zichzelf, maar werken ook onderling op elkaar in. Zo kunnen ervaringen met misbruik tijdens iemands jeugd het moeilijker maken om gezonde relaties met romantische partners te onderhouden, wat op zijn beurt tot weer andere problemen kan leiden. Hoe kunnen we deze complexe interacties tussen beschermende factoren, risicofactoren en veerkracht onderzoeken?

Een voorbeeld van hoe veerkracht kan worden gezien als een resultaat van complexe interacties komt uit het onderzoek naar ecosystemen. Ecosystemen worden bestudeerd als representaties van *complexe systemen*. Deze systemen bevatten verschillende elementen die op elkaar inwerken en zo in een toestand terecht kunnen

komen die zichzelf in stand houdt. Een goed voorbeeld van zo'n ecosysteem is een meer. Een meer bevat elementen zoals vissen, voedingsstoffen en algen, die allemaal van elkaar afhankelijk zijn. Het meer kan helder zijn, oftewel in een toestand zijn waarin alle elementen gedijen en een gezond evenwicht van vegetatie, vispopulatie en voedingsstoffen in stand wordt gehouden. Dit gezonde evenwicht kan echter worden verstoord, bijvoorbeeld wanneer de algen in het meer beginnen te groeien. Deze toename van het aantal algen kan het licht dat de bodem van het meer bereikt beperken, waardoor de vegetatie die er kan groeien afneemt. Deze afname van de vegetatie beperkt op haar beurt de vispopulatie en de voedingsstoffen, en leidt als zodanig tot troebel water in het meer. Deze causale keten van verstoringen is niet gemakkelijk omkeerbaar, en daarom wordt de situatie van troebel water opgevat als een zichzelf in stand houdende toestand. Een ecosysteem, zoals het meer, kan worden geïmplementeerd in een computationeel model en worden bestudeerd onder verschillende omstandigheden en *perturbaties* (d.w.z. stressoren of verstoringen) met behulp van simulaties, wat *simulatiemodellering* wordt genoemd. Deze aanpak is in de afgelopen decennia uitgebreid, bijvoorbeeld om inzicht te krijgen in de effecten van de klimaatcrisis op specifieke ecosystemen zoals regenwouden. Door uit het model toetsbare hypothesen te genereren, kan men de nauwkeurigheid van de voorspellingen nagaan en de modellen en theorieën verbeteren.

Deze benadering opent spannende mogelijkheden voor de studie van psychologische veerkracht. In dit proefschrift heb ik bestaande complexiteitsmodellen van psychopathologie gecombineerd met simulatiemodellen om een nieuw raamwerk te ontwikkelen voor het onderzoeken van psychologische veerkracht. De bestaande complexiteitsmodellen vinden hun oorsprong in de *netwerktheorie van de psychopathologie*, die stelt dat psychologische stoornissen zich gedragen als complexe systemen die georganiseerd zijn in een netwerk van onderling verbonden symptomen. Deze symptoomnetwerken kunnen zich in een gezonde toestand bevinden, wat betekent dat de meeste symptomen momenteel afwezig zijn, of zich ontwikkelen naar een stoornis-toestand, waarin veel symptomen geactiveerd zijn. Door de dynamiek van deze netwerken te bestuderen en gesimuleerde *klinische interventies* toe te voegen - die het netwerk naar een gezonde toestand trekken - of gesimuleerde *stressvolle verstoringen* toe te voegen- die het netwerk naar een stoornis-toestand trekken -, kunnen we onderzoeken hoe het symptoomnetwerk zich onder verschillende omstandigheden kan gedragen. Op die manier kunnen we de veerkracht van deze symptoomnetwerken, op basis van het gebruikte model, beoordelen.

De voorgestelde aanpak biedt een alternatief voor de eerder genoemde ethische en methodologische uitdagingen bij het bestuderen van veerkracht. In plaats van mensen aan echte tegenspoed bloot te stellen, kunnen we modellen gebruiken die de geestelijke gezondheid van mensen weergeven en deze modellen door middel van simulaties verstoren. Bovendien conceptualiseren deze complexiteitsmodellen

de onderlinge relaties tussen alle relevante factoren in plaats van veerkracht als één uitkomstvariabele te bestuderen. In het voorgestelde raamwerk is veerkracht dus geen entiteit binnen het netwerk (zoals een variabele die kan worden geïsoleerd), maar een *eigenschap* van het netwerk.

De bestaande symptoomnetwerken moeten echter op verschillende punten worden uitgebreid om bevindingen uit de onderzoeksliteratuur over veerkracht in dit nieuwe raamwerk te integreren. De hoofdstukken in dit proefschrift bespreken allemaal één van deze aspecten.

Hoofdstuk 2 laat zien hoe we de veerkracht van symptoomnetwerken met behulp van simulaties kunnen beoordelen. Complexe systemen produceren hun eigen gedragspatronen, afhankelijk van hoe de elementen van het systeem met elkaar samenhangen. Om het gedrag van een complex systeem te begrijpen, moeten we dus eerst de organisatie van het systeem begrijpen (d.w.z., welke knopen in het systeem zijn met elkaar verbonden, en hoe gemakkelijk worden deze knopen geactiveerd). Dit hoofdstuk laat zien hoe de architectuur van symptoomnetwerken samenhangt met hun veerkracht tegen verstoringen. De architectuur van een netwerk bestaat uit de *verbindingsgewichten* tussen de symptomen, die de sterkte van de verbindingen weergeven, en de *drempelwaarde* van elk symptoom, die hun dispositie voor activatie weergeven. Veerkrachtige netwerken worden over het algemeen gekenmerkt door hoge drempelwaarden en zwakke verbindingen tussen symptomen. Verschillende combinaties van verbindingsgewichten en drempelwaarden kunnen echter leiden tot hetzelfde veerkrachtniveau, wat wijst op de verschillende wegen waarlangs de veerkracht van een netwerk kan worden verbeterd. Opmerkelijk is dat de verschillen in parameterwaarden die resulteren in verschillende veerkrachtniveaus gering zijn. Dit verklaart mogelijk waarom veerkracht verondersteld wordt afhankelijk te zijn van complexe configuraties van factoren die veerkracht ondersteunen. Deze bevindingen worden gepresenteerd door het *veerkrachtkwadrant* te introduceren. Het veerkrachtkwadrant ordent symptoomnetwerken op basis van hun meest waarschijnlijke toestand (gezond of ongezond) en stabiliteit tegen verstoringen (stabiel of instabiel). Een veerkrachtig netwerk bevindt zich in een stabiele, gezonde toestand.

Hoofdstuk 3 vertrekt van netwerkmodellen van *psychologische stoornissen* naar modellen van *geestelijke gezondheid*, door symptoomnetwerken uit te breiden met externe risico- en beschermende factoren. Het hoofdstuk presenteert een formeel, complex systeem van geestelijke gezondheid dat ruimte biedt aan de factoren die in de onderzoeksliteratuur vaak in verband worden gebracht met de ontwikkeling van veerkracht. Het hoofdstuk stelt voor dat deze externe factoren specifieke parameters van het symptoomnetwerk kunnen veranderen, en als zodanig het netwerk kwetsbaarder of veerkrachtiger kunnen maken tegen verstoringen. Het hoofdstuk presenteert verschillende simulatiestudies die laten zien hoe dit proces eruit kan

zien. Op die manier kan veerkracht worden voorgesteld vanuit een multifactorieel perspectief waarin risico- en beschermende factoren met elkaar verbonden zijn en de aanwezigheid en stabiliteit van symptomen beïnvloeden.

Hoofdstuk 4 breidt het complexiteitsmodel van geestelijke gezondheid uit met langzame en snelle processen. De reden hiervoor is dat de verschillende risico- en beschermende factoren die van invloed zijn op veerkracht hoogstwaarschijnlijk op verschillende tijdschalen werken. Een voorbeeld van een langzaam proces dat van invloed kan zijn op de geestelijke gezondheid is persoonlijkheid. De persoonlijkheid van mensen kan veranderen, maar dit gebeurt in de loop van een mensenleven. Het is onwaarschijnlijk dat je op een persoonlijkheidstest van jaar tot jaar heel anders scoort, maar we verwachten meer verschillen wanneer je iemands testresultaten vergelijkt tussen een leeftijd van 20 jaar en 70 jaar. In het voorgestelde netwerkmodel van geestelijke gezondheid veranderen persoonlijkheidsfactoren (het langzame proces) de architectuur van het symptoomnetwerk van mentale stoornissen (het snelle proces) op een niet-triviale manier. We passen het model toe op de voorbeelden van neuroticisme (het trage proces) en depressie (het snelle proces). Het toegepaste model verbindt empirisch onderbouwde depressie en neuroticisme netwerken met elkaar. Dit geïntegreerde theoretische model laat zien dat simulaties resulteren in plausibele empirische patronen. Dit hoofdstuk is geïmplementeerd in een online simulatie-*tool* om de gepresenteerde studie eenvoudig te begrijpen en te repliceren.

In hoofdstuk 5 wordt onderzocht hoe risico- en beschermende factoren kunnen interacteren met de ontwikkeling van depressieve klachten. De studie in dit hoofdstuk richt zich op de wisselwerking tussen fluctuaties in positief en negatief affect, en de ontwikkeling van depressieve klachten. Deze wisselwerking wordt over een langere periode bekeken, zowel binnen dezelfde individuen, als tussen verschillende individuen. We analyseerden gegevens van 228 deelnemers die ten minste 20 assessments aflegden over een periode van 9-14 weken. We hebben longitudinale netwerken geschat, inclusief positief affect, negatief affect, en depressieve klachten. We vonden dat mensen die vertegenwoordigd werden door sterker verbonden netwerken (meer en sterkere verbindingen tussen de variabelen), ofwel een verlichting ofwel een verergering van depressieve klachten vertoonden in de loop van de tijd. Dit betekent dat de *dichtheid* van netwerkmodellen de fluctuaties van de variabelen over tijd zou kunnen tonen, wanneer wordt ingezoomd op individuele trajecten.

Hoofdstuk 6 presenteert een nieuwe methode en bijbehorend R-pakket (*nodeIdentifyR*) om de geprojecteerde effecten van symptoom-specifieke interventies in symptoomnetwerken te bestuderen. Het effect van een symptoom-specifieke interventie wordt berekend door het gedrag van het gehele netwerk te beschouwen. De methode kan worden toegepast op empirisch geschatte symptoomnetwerken om te identificeren welke specifieke symptomen de optimale *targets* zouden zijn

voor therapeutische interventies. Bovendien kan de methode bestuderen welke symptoom-specifieke stressvolle verstoring het meest ongunstige effect zou hebben op het netwerk. Dit zou informatie kunnen opleveren over de kwetsbaarheden in het netwerk die mogelijk in aanmerking moeten worden genomen voor preventieve zorg. Door een complexiteitsbenadering aan te nemen waarbij de effecten van gerichte interventies op het gedrag van het hele netwerk worden bestudeerd, anticipeert de methode op voortdurende effecten die zonder simulaties moeilijk te identificeren zijn.

Tot slot geeft hoofdstuk 7 de algemene discussie van het proefschrift met een overzicht van de uitdagingen om het voorgestelde raamwerk verder te ontwikkelen. Bijvoorbeeld, het ontwikkelen van nieuwe complexiteit (netwerk) modellen die over tijd kunnen variëren om beter te begrijpen hoe mensen veerkracht ontwikkelen. Daarnaast zou toekomstig onderzoek zich meer kunnen richten op de beschermende mechanismen die veerkracht verbeteren. Hoewel dit proefschrift de symptoomnetwerken vanuit methodologisch en conceptueel oogpunt heeft opengesteld voor het opnemen van positieve mentale gezondheidsvariabelen, heeft het deze variabelen niet vanuit een inhoudelijk oogpunt bestudeerd. Toekomstig onderzoek kan het voorgestelde raamwerk gebruiken om onze focus te verbreden van symptoomontwikkeling naar de ontwikkeling van beschermende factoren en veerkrachtmechanismen. Verder is meer onderzoek nodig om het voorgestelde raamwerk toe te passen op intra-individuele processen, zodat we de veerkracht van een individueel netwerk kunnen beoordelen. Tenslotte is de volgende stap in de verdere ontwikkeling van dit raamwerk de empirische validatie van zowel complexiteitsmodellen, specifiek, de netwerkmodellen, als de gesimuleerde dynamieken zoals voorgesteld in dit proefschrift. In dit hoofdstuk geef ik een overzicht van verschillende opties om met deze validaties te beginnen.

In dit proefschrift heb ik een raamwerk ontwikkeld om psychologische veerkracht te onderzoeken vanuit een complex systeemperspectief met behulp van simulaties. Het raamwerk opent nieuwe mogelijkheden voor het beoordelen van de veerkracht van symptoomnetwerken en laat verschillende mogelijkheden zien voor het uitbreiden van deze modellen om de onderzoeksliteratuur over veerkracht te accommoderen. Het raamwerk zou echter ook in bredere zin gebruikt kunnen worden in andere domeinen, zoals grotere gedragstransities buiten de context van de geestelijke gezondheidszorg. Een modelbenadering die verschillende scenario's bestudeert, kan helpen om te begrijpen hoe verschillende interventies kunnen uitpakken, aangezien deze niet los van elkaar kunnen worden begrepen. Men zou kunnen onderzoeken hoe lange termijn, stabiele gedragstransities in de samenleving (bv. de duurzame energietransitie) kunnen worden bereikt met behulp van het voorgestelde kader. Het onderzoeken van veerkracht als een eigenschap van complexe systemen door middel van simulaties zou op die manier wegen kunnen openen naar veel nieuwe en interessante onderzoeksprogramma's.

J

PUBLICATIONS

Chapter 1 is party adapted from the following book chapter:

Lunansky, G., Nuijten, M., Deserno, M., Cramer, A. O. J. & Borsboom, D. (2017). Een symptoom komt nooit alleen: Psychologische stoornissen als complexe netwerken. Chapter in: Handboek Psychopathologie; Eurelings-Bontekoe, E. H. M., Verheul, R. & Snellen, W. Bohn Stafleu van Loghum: Amsterdam

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GL designed the simulation study and wrote the draft of the manuscript, CDvB, TFB, AOJC & DB revised several (ok, many) versions of the manuscript. CDvB & DB supervised the simulations.

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GL designed the simulation studies and wrote the draft of the manuscript. MAvdL wrote the historical overview section in the introduction. CJG & MJE provided the empirical data. JMBH supervised simulation study 3. CDvB, JMBH, MAvdL & DB revised several versions of the manuscript.

Chapter 4 is published as:

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GL wrote the manuscript, CDvB & DB supervised the simulations and revised several versions of the manuscript.

An interactive, online summary of the chapter:
https://gabylunansky.shinyapps.io/PRPmodel/

GL developed the online Shiny application.

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**Shared first authorship*
GL, RHAH & TFB all designed the study, wrote and revised the manuscript.

Chapter 6 is published as:

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GL wrote the manuscript, JN was the main developer of the NIRA algorithm, CC & LW provided the data. JN, CDvB, CC & DB revised several versions of the manuscript.

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GL wrote the chapter, SE & AMI revised the chapter.

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K

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