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Intervening on psychopathology networks: Evaluating intervention targets through simulations

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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.

1. Introduction

Recent research focuses on the distinct roles that symptoms may play in the development of psychopathology [1]. 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") [2]. 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 [3,4]. 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) [5]. In the case of Major Depressive Disorder (MDD), specific treatment programs have been developed for suicidal behavior [6]. Symptom-specific interventions are also being developed in clinical trials, such as particular CBT for psychosis which focuses on treating hallucinations or delusions [7]. Furthermore, symptom-specific treatments are used in experimental settings, such as randomized controlled trials, to compare the specific

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effects of different treatment conditions, for example, between psychotherapy and psychopharmacology [8]. By using novel technology, "micro-interventions" can be administered via smartphones as a personalized approach to target the depressed mood symptom [9]. However, it is vital to consider the propelling effects from intervening on one symptom to other symptoms due to their potential interrelatedness [4].

An established framework to study psychopathology as an interrelated, dynamic system of symptoms is the network theory of mental disorders [2,10]. The network theory of psychopathology has been applied to a variety of psychiatric disorders (e.g., for MDD, see [11], for GAD, see [12], for Post-Traumatic Stress Disorder, see [13], for Psychosis, see [14]; and for Autism Spectrum Disorder, see [15]). 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 [1,10].

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 [16–18]). In these network models, *nodes* represent symptoms, and *edges* represent the unique associations between symptoms (see Fig. 1 [2,17]). Edge parameters are called edge weight parameters 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 [19]. 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 [2,10]. 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) [17], 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 [18,20] 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 [18,21–23]). A symptom with a strong disposition to be "off', for example, 'suicidal ideation', requires much 'input' such as stress before it will manifest.

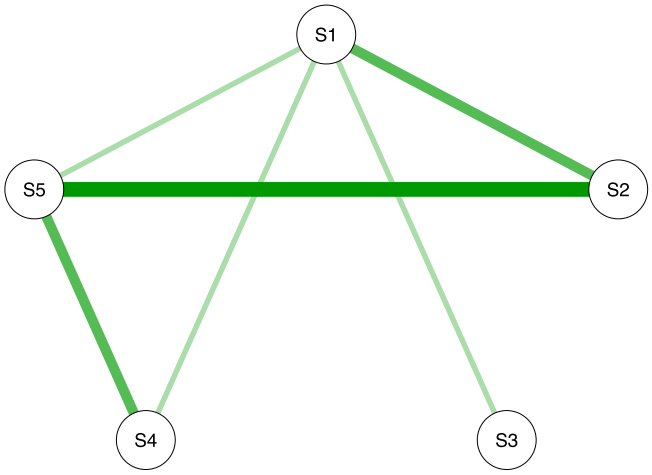

Fig. 1. Example of a Symptom Network Model Note. A hypothetical symptom network model for five psychopathology symptoms (S1-S5). Circles in the network represent nodes, which refer to the symptom variables (S1-S5). Lines that connect the circles represent edges, where green lines represent positive associations. 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). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

To assess the relative importance of symptoms in psychopathology networks estimated from observational data, the concept of *node centrality* was received with high hopes [24]. 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 [25]. The concept was translated to psychology [26], 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 [27]. Therefore, centrality metrics are used in psychopathology networks to identify possible intervention targets [2,19,24,28,29]. However, several researchers have raised doubts regarding the suitability of centrality indices in psychological networks [24,30–34]. 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 [31,35,36].

A developing novel tradition studies the projected influences of symptoms in psychopathology models using simulated symptom-specific perturbations as *in silico* interventions [33,35,37,38]. 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: [33,35,37]). 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 [37].

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 [39]. 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 paper 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.

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.

2.1. NodeIdentifyR algorithm

We present the *NodeIdentifyR* algorithm (NIRA) to identify the projected most efficient, symptom-specific intervention target in psychological networks[1]. 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.

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; [40]). Since the model's characteristics align with the network theory of psychopathology, it is often used as a statistical model of symptom networks [23,41]. 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 [11]). The Ising model uses binary data, meaning that symptoms can be "present" or "absent".

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 [18,23]. The intercept of the logistic regression represents the *threshold parameter* of every symptom, which denotes the symptom's disposition for manifestation [18,23]. Positive (negative) thresholds denote the symptom's disposition to be activated (deactivated) if all other symptoms are absent[2] [42]. 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 Appendix C details on the Ising model's dynamics.

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 $\times$ 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* [43], 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 [43]. 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 $\sim$ ten nodes) with the function *IsingLikelihood*, but this is infeasible for larger networks due to the intractability of the Ising model [43].

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 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 Appendix A 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., [44]. Multiple iterations are necessary to ensure that the simulated behavior is robust and replicable [45]. 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 Appendix B for stability analyses of NIRA using various numbers of iterations).

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

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

[2] 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 [22] for an extensive discussion.

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 [46]. 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.

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?

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; [47]), 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 [48]. 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.

2.2.2. Design

NIRA uses the *IsingFit* R package [41] to estimate the Ising Models and the *qgraph* R package [49] 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.

2.2.3. Comparison with strength centrality

Node centrality indices, precisely *strength centrality*, are calculated using the *qgraph* R package [49]. 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 [26]. 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 [34]. 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 [19]. We will therefore compute the correlation between strength centrality and NIRA.

3. Results

Fig. 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 1).

3.1. Interventions

First, NIRA was applied to the Ising model using alleviating interventions (see Fig. 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 Fig. 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

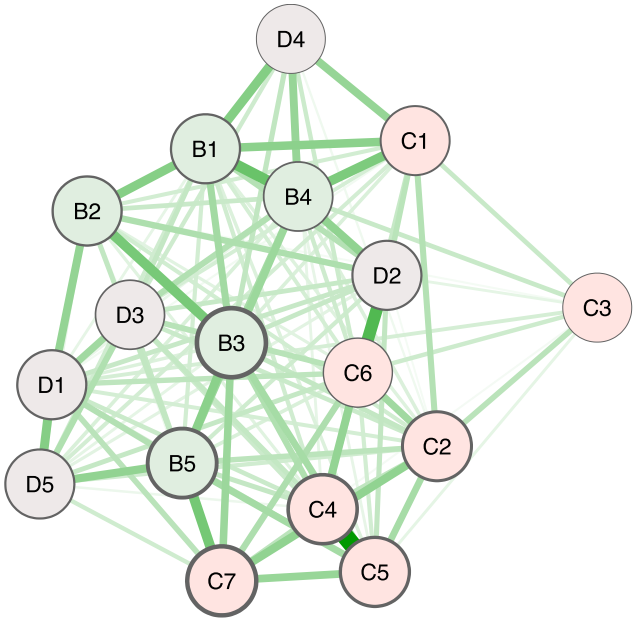

Fig. 2. Estimated Ising network model for 17 PTSD Symptoms in the Wenchuan earthquake study (N = 4910). Note. Nodes in the networks represent the 17 PTSD symptoms. Symptoms are grouped by color based on their clinical subdomain (Intrusion, Avoidance, and Arousal). The thickness of node borders represents 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).

Table 1
PTSD Symptoms, their corresponding domains and prevalence

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

Note. The table shows all 17 PTSD symptoms from the empirical illustration and their corresponding domains. Furthermore, it 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.

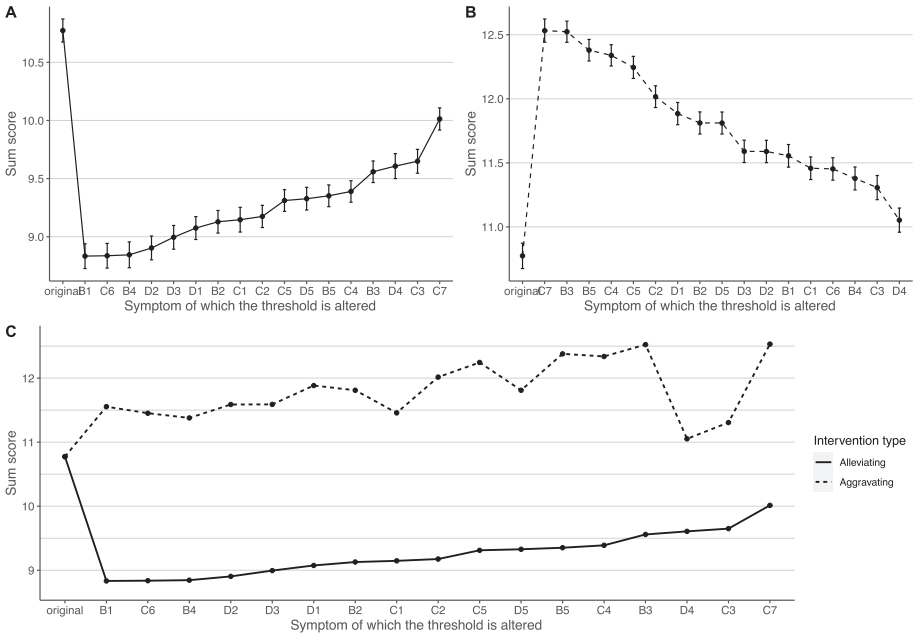

Fig. 3. Projected Effects of NIRA Interventions to the PTSD Ising Model Note. Panel A shows results after alleviating interventions (black lines), panel B after aggravating interventions (dashed lines), and panel C compares results from both intervention types. The black dots represent the network's 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.

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.

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 Fig. 3; panel C). The results in Fig. 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.

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 Fig. 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.

3.2. Comparing strength centrality and NIRA

Fig. 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 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.

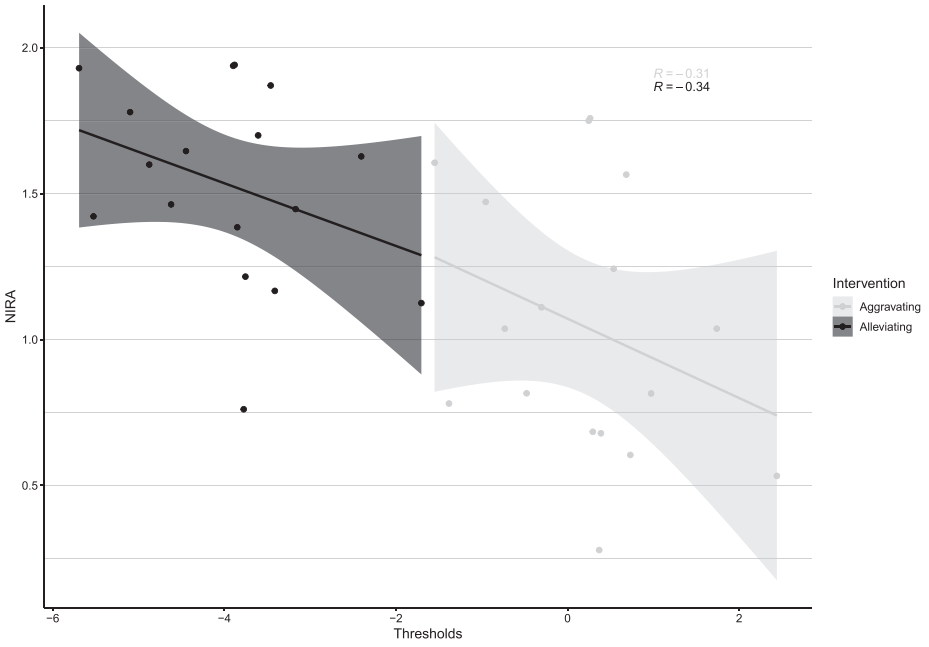

Fig. 4. The Relation between Threshold Magnitudes and NIRA Outcomes after Interventions Note. The x-axis shows the magnitude of the threshold parameters after interventions for both alleviating interventions (black) and aggravating interventions (grey). The y-axis shows the NIRA outome, computed as the 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.

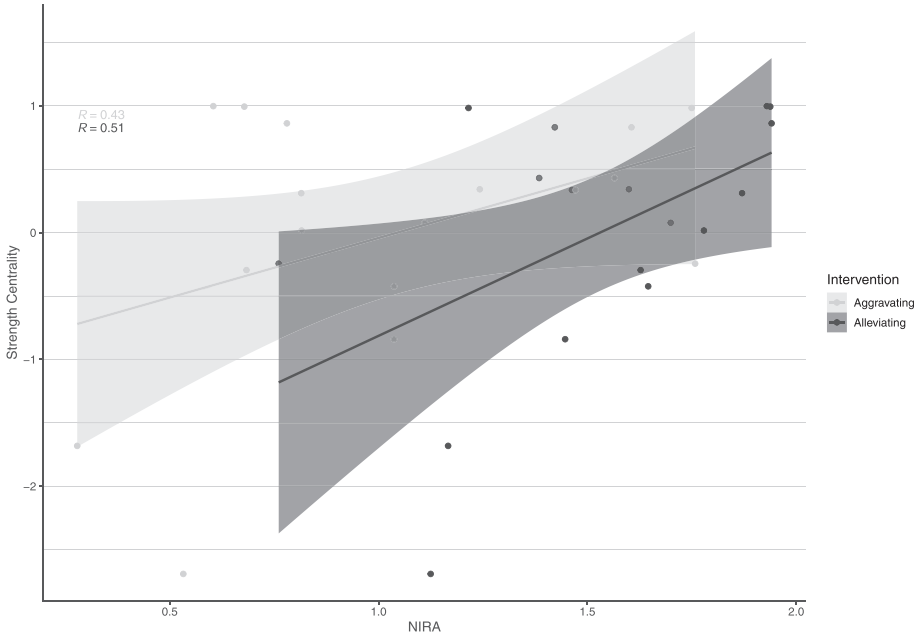

Fig. 5. Comparing Strength Centrality with Interventions from NIRA Note. The relation between node strength centrality and projected effects from NIRA interventions for alleviating interventions (black) and aggravating interventions (grey). The area around the lines represents the 95% confidence interval.

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 [2,10,11]. 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.

Table 2
Comparison Between Strength Centrality and NIRA Interventions

Centrality		NIRA			
Strength		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

Note. 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.

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 automatically 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 [50]).

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 the remaining 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 [40]. 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 [16] or GGM [17]. 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 [40]. 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 [36,38,51]– [55] or psychological capacities [56]. 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 [52,54]. 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 [53]. 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 Appendix A 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. [57], who adhere different values to the symptom variables in the Ising model. A symptom with a solid projected influence, such as insomnia [58], 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 [59]. For example, treatment interventions aiming to decrease the 'depressed mood' symptom of a patient may focus on changing maladaptive thought patterns [38]. 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 [60]. Some argue that mental states are too overlapping to be considered suitable intervention targets [61]. In other words, the interdependence of symptoms implies their inseparability, rendering it impossible to separate unique contributions of symptoms [62]. In the current paper, 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* [63] see Fig. 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 [23]. 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. [23], specifically, Fig. 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 [64–66]. 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 [66]. 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 [67,68]. IRF is used in economics (see, for example, [69], 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 [70].

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.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] T.F. Blanken, M.K. Deserno, J. Dalege, D. Borsboom, P. Blanken, G.A. Kerkhof, A.O. J. Cramer, The role of stabilizing and communicating symptoms given overlapping communities in psychopathology networks, Sci. Rep. 8 (1) (2018), https://doi.org/10.1038/s41598-018-24224-2.

[2] D. Borsboom, A.O.J. Cramer, Network Analysis: An Integrative Approach to the Structure of Psychopathology, Annu. Rev. Clin. Psychol. 9 (1) (2013) 91–121, https://doi.org/10.1146/clinpsy.2013.9.issue-110.1146/annurev-clinpsy-050212-185608.

[3] A.M. Chekroud, R. Gueorguieva, H.M. Krumholz, M.H. Trivedi, J.H. Krystal, G. McCarthy, Reevaluating the efficacy and predictability of antidepressant treatments: A symptom clustering approach, JAMA Psychiatry 74 (4) (Apr. 2017) 370–378, https://doi.org/10.1001/jamapsychiatry.2017.0025.

[4] L. Boschloo, E. Bekhuis, E.S. Weitz, M. Reijnders, R.J. DeRubeis, S. Dimidjian, D. L. Dunner, B.W. Dunlop, U. Hegerl, S.D. Hollon, R.B. Jarrett, S.H. Kennedy, J. Miranda, D. Mohr, A.D. Simons, G. Parker, F. Petrak, S. Herpertz, L.C. Quilty, A. John Rush, Z.V. Segal, J.R. Vittengl, R.A. Schoevers, P. Cuijpers, The symptom-specific efficacy of antidepressant medication vs. cognitive behavioral therapy in the treatment of depression: results from an individual patient data meta-analysis, World Psychiatry 18 (2) (2019) 183–191, https://doi.org/10.1002/wps.v18.210.1002/wps.20630.

[5] M.J. Dugas, R. Ladouceur, Treatment of GAD: Targeting intolerance of uncertainty in two types of worry, Behav. Modif. 24 (5) (Jul. 2000) 635–657, https://doi.org/10.1177/0145445500245002.

[6] C.R. DeCou, K.A. Comtois, S.J. Landes, Dialectical Behavior Therapy Is Effective for the Treatment of Suicidal Behavior: A Meta-Analysis, Behav. Ther. 50 (1) (Jan. 2019) 60–72, https://doi.org/10.1016/j.beth.2018.03.009.

[7] T.M. Lincoln, E. Peters, A systematic review and discussion of symptom specific cognitive behavioural approaches to delusions and hallucinations, Schizophr. Res. 203 (Jan. 2019) 66–79, https://doi.org/10.1016/j.schres.2017.12.014.

[8] E. Bekhuis *et al.*, "Symptom-Specific Effects of Psychotherapy versus Combined Therapy in the Treatment of Mild to Moderate Depression: A Network Approach," *Psychother. Psychosom.*, vol. 87, no. 2, pp. 121–123, Mar. 2018, doi: 10.1159/000486793.

[9] G. Meinlschmidt *et al.*, "Smartphone-based psychotherapeutic micro-interventions to improve mood in a real-world setting," *Front. Psychol.*, vol. 7, no. JUL, p. 1112, Jul. 2016, doi: 10.3389/fpsyg.2016.01112.

[10] D. Borsboom, A network theory of mental disorders, World Psychiatry 16 (1) (Feb. 2017) 5–13, https://doi.org/10.1002/wps.20375.

[11] A. O. J. Cramer *et al.*, "Major Depression as a Complex Dynamic System," *PLoS One*, vol. 11, no. 12, p. e0167490, Dec. 2016, doi: 10.1371/journal.pone.0167490.

[12] C. Beard, A.J. Millner, M.J.C. Forgeard, E.I. Fried, K.J. Hsu, M.T. Treadway, C. V. Leonard, S.J. Kertz, T. Björgvinsson, Network analysis of depression and anxiety symptom relationships in a psychiatric sample, Psychol. Med. 46 (16) (2016) 3359–3369, https://doi.org/10.1017/S0033291716002300.

[13] C. Armour, E. I. Fried, and M. Olff, "European Journal of Psychotraumatology PTSD symptomics: network analyses in the field of psychotraumatology," 2017, doi: 10.1080/20008198.2017.1398003.

[14] A.-M. Isvoranu, C.D. van Borkulo, L.-L. Boyette, J.T.W. Wigman, C.H. Vinkers, D. Borsboom, A Network Approach to Psychosis: Pathways Between Childhood Trauma and Psychotic Symptoms, Schizophr. Bull. 43 (1) (2017) 187–196, https://doi.org/10.1093/schbul/sbw055.

[15] M. K. Deserno, D. Borsboom, S. Begeer, and H. M. Geurts, "Relating ASD symptoms to well-being: moving across different construct levels," 2017, doi: 10.1017/S0033291717002616.

[16] J. M. B. Haslbeck and L. J. Waldorp, "mgm: Estimating Time-Varying Mixed Graphical Models in High-Dimensional Data," *J. Stat. Softw.*, vol. 93, no. 8, Oct. 2020, Accessed: Apr. 13, 2020. [Online]. Available: http://arxiv.org/abs/1510.06871.

[17] S. Epskamp, L.J. Waldorp, R. Mõttus, D. Borsboom, The Gaussian Graphical Model in Cross-Sectional and Time-Series Data, Multivariate Behav. Res. 53 (4) (2018) 453–480, https://doi.org/10.1080/00273171.2018.1454823.

[18] C. D. van Borkulo, D. Borsboom, and S. Epskamp, "A new method for constructing networks from binary data," *Sci. Rep.*, 2014, Accessed: Apr. 13, 2020. [Online]. Available: https://www.nature.com/articles/srep05918.

[19] S. Epskamp, D. Borsboom, E.I. Fried, Estimating psychological networks and their accuracy: A tutorial paper, Behav. Res. Methods 50 (1) (Feb. 2018) 195–212, https://doi.org/10.3758/s13428-017-0862-1.

[20] S. Epskamp, E.I. Fried, A tutorial on regularized partial correlation networks, Psychol. Methods 23 (4) (Dec. 2018) 617–634, https://doi.org/10.1037/met0000167.

[21] J.M.B. Haslbeck, S. Epskamp, M. Marsman, L.J. Waldorp, Interpreting the Ising Model: The Input Matters, Multivariate Behav. Res. 56 (2) (2021) 303–313, https://doi.org/10.1080/00273171.2020.1730150.

[22] M. Marsman *et al.*, "An Introduction to Network Psychometrics: Relating Ising Network Models to Item Response Theory Models," *https://doi.org/10.1080/00273171.2017.1379379*, vol. 53, no. 1, pp. 15–35, Jan. 2017, doi: 10.1080/00273171.2017.1379379.

[23] M. Marsman, D. Borsboom, J. Kruis, S. Epskamp, R. van Bork, L.J. Waldorp, H.L.J. V.D. Maas, G. Maris, An Introduction to Network Psychometrics: Relating Ising Network Models to Item Response Theory Models, Multivariate Behav. Res. 53 (1) (2018) 15–35, https://doi.org/10.1080/00273171.2017.1379379.

[24] T. R. Spiller, O. Levi, Y. Neria, B. Suarez-Jimenez, Y. Bar-Haim, and A. Lazarov, "On the validity of the centrality hypothesis in cross-sectional between-subject networks of psychopathology," *BMC Med.*, vol. 18, no. 1, p. 297, Oct. 2020, doi: 10.1186/s12916-020-01740-5.
[25] M.E.J. Newman, in: Networks, Oxford University Press, 2010, pp. 1–14, https://doi.org/10.1093/acprof:oso/9780199206650.003.0001.
[26] A. O. J. Cramer, L. J. Waldorp, H. L. J. van der Maas, and D. Borsboom, "Comorbidity: A network perspective," *Behavioral and Brain Sciences*, vol. 33, no. 2–3. Cambridge University Press, pp. 137–150, 2010, doi: 10.1017/S0140525X09991567.
[27] D. Robinaugh, R.H.A. Hoekstra, E.R. Toner, D. Borsboom, The network approach to psychopathology: a review of the literature 2008–2018 and an agenda for future research, Psychol. Med. 50 (3) (2020) 353–366, https://doi.org/10.1017/S0033291719003404.
[28] J. Stochl, E. Soneson, A.P. Wagner, G.M. Khandaker, I. Goodyer, P.B. Jones, Identifying key targets for interventions to improve psychological wellbeing: replicable results from four UK cohorts, Psychol. Med. 49 (14) (2019) 2389–2396, https://doi.org/10.1017/S0033291718003288.
[29] E. I. Fried *et al.*, "Replicability and Generalizability of Posttraumatic Stress Disorder (PTSD) Networks: A Cross-Cultural Multisite Study of PTSD Symptoms in Four Trauma Patient Samples.," *Clin. Psychol. Sci. a J. Assoc. Psychol. Sci.*, vol. 6, no. 3, pp. 335–351, May 2018, doi: 10.1177/2167702617745092.
[30] L.F. Bringmann, T. Elmer, S. Epskamp, R.W. Krause, D. Schoch, M. Wichers, J.T. W. Wigman, E. Snippe, What Do Centrality Measures Measure in Psychological Networks? J. Abnorm. Psychol. 128 (8) (2019) 892–903, https://doi.org/10.1037/abn0000446.
[31] F. Dablander, M. Hinne, Node centrality measures are a poor substitute for causal inference, Sci. Rep. 9 (1) (2019) 1–13, https://doi.org/10.1038/s41598-019-43033-9.
[32] M. N. Hallquist, A. G. C. Wright, and P. C. M. Molenaar, "Problems with Centrality Measures in Psychopathology Symptom Networks: Why Network Psychometrics Cannot Escape Psychometric Theory," *Multivariate Behav. Res.*, pp. 1–25, Aug. 2019, doi: 10.1080/00273171.2019.1640103.
[33] D. Castro, F. Ferreira, I. de Castro, A.R. Rodrigues, M. Correia, J. Ribeiro, T. B. Ferreira, The Differential Role of Central and Bridge Symptoms in Deactivating Psychopathological Networks, Front. Psychol. 10 (2019), https://doi.org/10.3389/fpsyg.2019.0244810.3389/fpsyg.2019.02448.s001.
[34] T.L. Rodebaugh, N.A. Tonge, M.L. Piccirillo, E. Fried, A. Horenstein, A.S. Morrison, P. Goldin, J.J. Gross, M.H. Lim, K.C. Fernandez, C. Blanco, F.R. Schneier, R. Bogdan, R.J. Thompson, R.G. Heimberg, Does centrality in a cross-sectional network suggest intervention targets for social anxiety disorder? J. Consult. Clin. Psychol. 86 (10) (2018) 831–844, https://doi.org/10.1037/ccp0000336.
[35] T.R. Henry, D.J. Robinaugh, E.I. Fried, On the control of psychological networks, PsyArXiv (2020) 1–30, https://doi.org/10.31234/osf.io/7vpz2.
[36] J.M.B. Haslbeck, O. Ryan, D.J. Robinaugh, L.J. Waldorp, D. Borsboom, "Modeling Psychopathology, From Data Models to Formal Theories" (2019).
[37] Robinaugh, A. J. Millner, and R. J. McNally, "Identifying highly influential nodes in the complicated grief network," *J. Abnorm. Psychol.*, vol. 125, no. 6, pp. 747–757, Aug. 2016, doi: 10.1037/abn0000181.
[38] J. Burger *et al.*, "Bridging the gap between complexity science and clinical practice by formalizing idiographic theories: a computational model of functional analysis," *BMC Med.*, vol. 18, no. 99, 2020, doi: 10.1186/s12916-020-01558-1.
[39] J. Barth, T. Munder, H. Gerger, E. Nüesch, S. Trelle, H. Znoj, P. Jüni, P. Cuijpers, Comparative Efficacy of Seven Psychotherapeutic Interventions for Patients with Depression: A Network Meta-Analysis, Focus (Madison) 14 (2) (2016) 229–243, https://doi.org/10.1176/appi.focus.140201.
[40] E. Ising, Beitrag zur theorie des ferromagnetismus, Zeitschrift für Phys. 31 (1) (1925) 253–258.
[41] C.D. van Borkulo, S. Epskamp, A. Robitzsch, IsingFit: Fitting Ising models using the eLasso method, R Packag. version (2014) 2.
[42] J. Dalege, D. Borsboom, F. van Harreveld, H.L.J. van der Maas, The Attitudinal Entropy (AE) Framework as a General Theory of Individual Attitudes, Psychol. Inq. 29 (4) (2018) 175–193, https://doi.org/10.1080/1047840X.2018.1537246.
[43] S. Epskamp, "IsingSampler: Sampling Methods and Distribution Functions for the Ising Model." 2020.
[44] A.F. Danvers, R. Wundrack, M. Mehl, Equilibria in Personality States: A Conceptual Primer for Dynamics in Personality States, Eur. J. Pers. 34 (6) (2020) 999–1016, https://doi.org/10.1002/per.2239.
[45] J.P. Nilmeier, G.E. Crooks, D.D.L. Minh, J.D. Chodera, Nonequilibrium candidate Monte Carlo is an efficient tool for equilibrium simulation, Proc. Natl. Acad. Sci. U. S. A. 108 (45) (2011) E1009–E1018, https://doi.org/10.1073/pnas.1106094108.
[46] J. Dalege, D. Borsboom, F. van Harreveld, H.L.J. van der Maas, Network Analysis on Attitudes: A Brief Tutorial, Soc. Psychol. Personal. Sci. 8 (5) (Jul. 2017) 528–537, https://doi.org/10.1177/1948550617709827.
[47] A.M. Steinberg, M.J. Brymer, K.B. Decker, R.S. Pynoos, The University of California at Los Angeles Post-traumatic Stress Disorder Reaction Index, Curr. Psychiatry Rep. 6 (2) (2004) 96–100.
[48] J.L. Schafer, J.W. Graham, Missing data: Our view of the state of the art, Psychol. Methods 7 (2) (2002) 147–177, https://doi.org/10.1037/1082-989X.7.2.147.
[49] S. Epskamp, A. O. J. Cramer, L. J. Waldorp, V. D. Schmittmann, and D. Borsboom, "Qgraph: Network visualizations of relationships in psychometric data," *J. Stat. Softw.*, vol. 48, no. 4, pp. 1–18, 2012, Accessed: Apr. 13, 2020. [Online]. Available: http://www.jstatsoft.org/.
[50] L. Solá, M. Romance, R. Criado, J. Flores, A. García del Amo, S. Boccaletti, Eigenvector centrality of nodes in multiplex networks, Chaos 23 (3) (2013) 033131, https://doi.org/10.1063/1.4818544.
[51] E.I. Fried, Theories and Models: What They Are, What They Are for, and What They Are About, Psychological Inquiry 31 (4) (2020) 336–344, https://doi.org/10.1080/1047840X.2020.1854011.
[52] O. Guest and A. E. Martin, "How computational modeling can force theory building in psychological science," 2020.
[53] D. Borsboom, H. van der Maas, J. Dalege, R. Kievit, and B. Haig, "Theory Construction Methodology: A practical framework for theory formation in psychology," 2020, doi: 10.31234/osf.io/w5tp8.
[54] D. Robinaugh, J. Haslbeck, O. Ryan, E. Fried, and L. Waldorp, "Invisible Hands and Fine Calipers: A Call to Use Formal Theory as a Toolkit for Theory Construction," 2020, doi: 10.31234/osf.io/ugz7y.
[55] G. Schiepek, A dynamic systems approach to clinical case formulation, Eur. J. Psychol. Assess. 19 (3) (2003) 175–184, https://doi.org/10.1027/1015-5759.19.3.175.
[56] I. van Rooij and G. Baggio, "Theory Before the Test: How to Build High-Verisimilitude Explanatory Theories in Psychological Science.," *Perspect. Psychol. Sci.*, p. 1745691620970604, Jan. 2021, doi: 10.1177/1745691620970604.
[57] Kruis, J. (2020). Transformations of mixed spin-class Ising systems. *arXiv preprint arXiv:2006.13581*.
[58] T.F. Blanken, T. Van Der Zweerde, A. Van Straten, E.J.W. Van Someren, D. Borsboom, J. Lancee, Introducing Network Intervention Analysis to Investigate Sequential, Symptom-Specific Treatment Effects: A Demonstration in Co-Occurring Insomnia and Depression, Psychother. Psychosom. 88 (1) (2019) 52–54, https://doi.org/10.1159/000495045.
[59] R.J. McNally, Network Analysis of Psychopathology: Controversies and Challenges, Annu. Rev. Clin. Psychol. 17 (2021) 31–53, https://doi.org/10.1146/annurev-clinpsy-081219.
[60] N.S. de Boer, L.C. de Bruin, J.J.G. Geurts, G. Glas, The Network Theory of Psychiatric Disorders: A Critical Assessment of the Inclusion of Environmental Factors, Front. Psychol. 12 (2021), 623970, https://doi.org/10.3389/fpsyg.2021.623970.
[61] J. Woodward, Cause and explanation in psychiatry: an interventionist perspective, in: K.S. Kendler, J. Parnas (Eds.), Philosophical issues in psychiatry: Explanation, phenomenology and nosology, John Hopkins University Press, Baltimore, 2014, pp. 209–272.
[62] M. Olthof, F. Hasselman, F. O. Maatman, A. Bosman, and A. Lichtwarck-Aschoff, "Complexity Theory of Psychopathology," doi: 10.31234/OSF.IO/F68EJ.
[63] S. Epskamp, M. Rhemtulla, and D. Borsboom, "Generalized Network Psychometrics: Combining Network and Latent Variable Models," *Psychom. 2017 824*, vol. 82, no. 4, pp. 904–927, Mar. 2017, doi: 10.1007/S11336-017-9557-X.
[64] P.C.M. Molenaar, A Manifesto on Psychology as Idiographic Science: Bringing the Person Back Into Scientific Psychology, This Time Forever, Meas. Interdiscip. Res. Perspect. 2 (4) (2004) 201–218, https://doi.org/10.1207/s15366359mea0204_1.
[65] E.L. Hamaker, Why researchers should think 'within-person': A paradigmatic rationale, in: M.R. Mehl, T.S. Conner (Eds.), Handbook of research methods for studying daily, The Guilford Press, 2012, pp. 43–61.
[66] L. F. Bringmann *et al.*, "A Network Approach to Psychopathology: New Insights into Clinical Longitudinal Data," *PLoS One*, vol. 8, no. 4, Apr. 2013, doi: 10.1371/journal.pone.0060188.
[67] H. Lütkepohl, A. Staszewska-Bystrova, P. Winker, Comparison of methods for constructing joint confidence bands for impulse response functions, Int. J. Forecast. 31 (3) (2015) 782–798, https://doi.org/10.1016/j.ijforecast.2013.08.003.
[68] X. Yang, N. Ram, J.P. Lougheed, P.C.M. Molenaar, T. Hollenstein, Adolescents' emotion system dynamics: Network-based analysis of physiological and emotional experience, Dev. Psychol. 55 (9) (2019) 1982–1993, https://doi.org/10.1037/dev0000690.
[69] A. Inoue, L. Kilian, Inference on impulse response functions in structural VAR models, J. Econom. 177 (1) (2013) 1–13, https://doi.org/10.1016/j.jeconom.2013.02.009.
[70] P.E. Spector, Do Not Cross Me: Optimizing the Use of Cross-Sectional Designs, J. Bus. Psychol. 34 (2) (2019) 125–137, https://doi.org/10.1007/s10869-018-09613-8.