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RESEARCH ARTICLE

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Unraveling the comorbidity of depression and anxiety in a large inpatient sample: Network analysis to examine bridge symptoms

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Abstract

Background: Comorbidities in mental disorders are often understood by assuming a common cause. The network theory of mental disorders offers an alternative to this assumption by understanding comorbidities as mutually reinforced problems. In this study, we used network analysis to examine bridge symptoms between anxiety and depression in a large sample.

Method: Using data from a sample of patients diagnosed with both depression and an anxiety disorder before and after inpatient treatment ($N = 5{,}614$, mean age: 42.24, 63.59% female, average treatment duration: 48.12 days), network models of depression and anxiety symptoms are estimated. Topology, the centrality of nodes, stability, and changes in network structure are analyzed. Symptoms that drive comorbidity are determined by bridge node analysis. As an alternative to network communities based on categorical diagnosis, we performed a community analysis and propose empirically derived symptom subsets.

Results: The obtained network models are highly stable. Sad mood and the inability to control worry are the most central. Psychomotor agitation or retardation is the strongest bridge node between anxiety and depression, followed by concentration problems and restlessness. Changes in appetite and suicidality were unique to depression. Community analysis revealed four symptom groups.

Conclusion: The estimated network structure of depression and anxiety symptoms proves to be highly accurate. Results indicate that some symptoms are considerably more influential than others and that only a small number of predominantly physical symptoms are strong candidates for explaining comorbidity. Future studies should include physiological measures in network models to provide a more accurate understanding.

KEYWORDS

assessment/diagnosis, depression, International, measurement/psychometrics, phobia/phobic disorders

1 | INTRODUCTION

Anxiety disorders are a common comorbidity in patients with depressive disorders and vice versa. For example, one large, population-representative surveys show that 51% of people diagnosed with major depressive disorder (MDD) are also diagnosed with an anxiety disorder in the same year, compared to 11.8% in people without MDD (Olfson et al., 2017). For patients suffering from MDD and anxiety disorders, the following characteristics have also been discovered in studies that appear clinically significant: higher rates of functional impairment and suicidality were found in patients with MDD and comorbid anxiety disorders (Seo et al., 2011). Both pharmacotherapy and psychotherapy aimed at treating depression reduce comorbid anxiety symptoms compared to control groups (Cuijpers et al., 2013; Weitz et al., 2018). However, MDD patients with comorbid anxiety disorders are more likely to show antidepressant resistance (Andreescu et al., 2007; Chen et al., 2020) and poorer outcomes as well as higher rates of premature termination of treatment when receiving psychotherapy (C. Brown et al., 1996; Furukawa et al., 2018; Young et al., 2006).

Research on the foundations of comorbidity is traditionally conducted under the assumptions of the "common cause model" (CCM, Cramer et al., 2010; Frewen et al., 2013). Within this context, mental disorders are understood as distinct nosological entities that explain the presence and co-occurrence of symptoms. While mental disorders cannot be observed directly, symptoms are considered reflective of a common cause. The CCM approach has strong links to somatic medicine, where understandable pathogenic pathways can be observed. For example, it is assumed that symptoms of a cold—coughing, sneezing, runny nose—co-occur due to a viral infection of the upper respiratory tract (Lorber, 1996). Similarly, the co-occurrence of multiple depressive symptoms is explained by the presence of a latent disorder named "depression". Comorbidities between depressive and anxiety disorders are explained by the presence of a latent cause for both disorders. Notably, a general factor of psychopathology (the p-factor) has been proposed as an explanation of comorbidities of mental disorders (Caspi et al., 2014).

However, many problems arise when applying this approach to psychopathology. First, the search for a common pathogenic pathway in most mental disorders has so far been inconclusive despite considerable scientific efforts (Borsboom et al., 2019; Kendler et al., 2011). Second, CCM may obscure the specific associations between symptoms, even though functional associations between symptoms are part and parcel of clinical psychology (e.g. Ferster, 1973). The network theory of mental disorders (NT, Borsboom, 2017) was proposed as an alternative to CCM to overcome its shortcomings. NT understands mental disorders as sets of co-occurring problems that mutually influence and possibly reinforce each other. Instead of explaining the covariance of symptoms by a hierarchically superordinate common cause, this covariance is assumed to be constitutive for mental disorders (Borsboom & Cramer, 2013).

The most common method used for psychological network models is the Graphical Gaussian Model (GGM; Epskamp et al., 2016). The GGM can be estimated for continuous and ordinal data assumed to be normally distributed. GGM models of psychometric data consist of nodes representing the items and edges representing partial correlations that describe the relationship between two nodes after controlling for all other relationships in the network. The centrality, that is, the extent of the influence of individual nodes can be analyzed.

These properties of network models open up interesting possibilities for the investigation of comorbidity. For example, the examination of so-called "bridge nodes" (Jones et al., 2019), which are strongly connected with symptoms of other disorders, may provide more insights into the role of individual symptoms. Network analyses have been conducted for several comorbid disorders. For example, Jones et al. (2018) studied symptoms of MDD and obsessive-compulsive disorder and found that obsessive behavior and cognitions, as well as concentration problems, guilt, and sadness can best explain the high comorbidity rates between these disorders.

A recently published review of the first decade of network analysis studies (Robinaugh et al., 2020) concluded with an agenda for future research. The authors called for the evaluation of previously published exploratory findings using large samples. This should enable robust and reliable findings that can subsequently be used for formal theory building. As mentioned above, the comorbidity of anxiety and depression symptoms has already been investigated using network analysis by Beard et al. (2016). However, certain adjustments could be made to further the understanding of this topic. First, the sample was highly heterogenous regarding the diagnosis and included psychotic patients, cases of bipolar disorder, and patients with manic episodes. This heterogeneity makes it difficult to interpret and generalize the results and could have led to inaccurate estimates for two main reasons. First, patients that were not diagnosed with any of these disorders, so correlations between anxiety and depression symptoms could have been influenced by unmeasured variables from other problem areas. One salient example is alcohol use disorder: withdrawal could lead to an increase in both symptoms resembling depression (Brown & Schuckit, 1988) and anxiety, possibly inflating the correlation between corresponding symptoms. The more heterogeneous the sample, the more of these artificial correlations can occur. Second, patients with other primary diagnoses were probably treated neither for anxiety nor for depressive disorders. It remains unclear whether changes in network structure—or lack thereof—are due to the treatment of core symptoms of anxiety and depression, or due to changes in other problem areas that are not part of the network. We intend to limit heterogeneity as strongly as possible by including only patients suffering from both diagnoses. Thus, we include only patients diagnosed with both a depressive disorder and an anxiety disorder. Second, a regularization method was used to estimate networks that contain less spurious edges and are more generalizable. Recently, it was shown that nonregularized GGM has a lower false-positive rate and is more generalizable (Williams et al., 2019). Thus, we will estimate network models without regularization. Instead, the correction of significance levels and a forward-search procedure is employed (Williams & Rast, 2019). Third, node centrality was analyzed without taking into

account whether individual nodes belong to anxiety or depression communities. Bridge symptoms were identified by visual inspection. For a more precise understanding of comorbidity, however, a valid quantification of the relevance of each symptom is necessary. Thus, the aims of this study are as follows:

Aim 1: Modeling an accurate MDD/anxiety symptoms network structure.

Using a large sample of patients suffering from both MDD and anxiety disorders, we estimate the network structure of the accompanying symptoms, including network structures before and after treatment, changes of this structure throughout the treatment of centrality analyses. We also compare our results to findings from the smaller sample used by Beard et al. (2016).

Aim 2: Analysis of bridges between MDD and anxiety symptoms.

To add to previous findings, we perform bridge node analysis (Jones et al., 2019) on the estimated models. For this purpose, adjusted centrality measures are calculated that take into account the membership of the items in their respective communities. Only connections to items of the other community are considered in the calculation.

Aim 3: Proposal of an empirically derived community structure.

After identifying reasons for the frequent comorbidity of categorical diagnoses of anxiety disorders and depression, we propose network communities based on empirical evidence. We will perform a clique percolation community analysis (Palla et al., 2005) on the estimated network models, allowing us to detect more coherent communities that could lead to a better understanding of depressive and anxiety symptoms beyond diagnostic categories.

2 | METHODS

2.1 | Patients and treatment setting

In this study, we analyzed data routinely collected over 5 years from patients treated in five German clinics providing inpatient treatment for various psychiatric disorders from the F30–F60 spectrum (Schoen clinics) that offer specialized inpatient treatment. The patients completed various self-report questionnaires at admission and discharge and were interviewed by clinicians. All patients gave informed consent to anonymous evaluations of their routinely collected data. The routine clinical inpatient treatment consisted of multimodal, nonmanualized cognitive-behavioral psychotherapy and, if indicated, psychopharmacotherapy according to national guidelines for the evidence-based treatment of depression and anxiety disorders (Bandelow et al., 2014; Härter et al., 2010). The patients of our sample spent an average of 48.12 (SD = 16.48) days in treatment.

The size of the patient database was $N = 44{,}277$. However, for reasons discussed previously, the following inclusion and exclusion criteria had to be met:

- Presence of either a depressive disorder or dysthymia (ICD codes F32, F33, or F34.1) or an anxiety disorder (F40 or F41) as a primary diagnosis.
- If the primary diagnosis was a depressive disorder or dysthymia, an anxiety disorder as a secondary diagnosis needed to be present. This condition was met by 5601 patients.
- If the primary diagnosis was an anxiety disorder, a depressive disorder as a secondary diagnosis needed to be present. This condition was met by 1788 patients.
- Completion of patient health questionnaire-9 and generalized anxiety disorder-7 assessments at admission and discharge. After applying this criterion, data of 5614 patients could be analyzed.

Detailed sample characteristics can be found in Table 1.

2.2 | Measures

Several instruments assessed treatment outcomes and were administered both at admission and at discharge. To assess MDD and anxiety symptoms, two self-report questionnaires were used: the Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001) and the seven-item generalized anxiety disorder scale (GAD-7; Spitzer et al., 2006). The PHQ-9 assesses the nine criteria of Major Depression while the GAD-7 measures the main criteria of generalized anxiety disorder but is also used to assess the severity of other anxiety disorders. Patients rated their depression and anxiety symptoms on a scale from 0 (not at all) to 3 (nearly every day). Both measures are well-validated screening and severity measures for a wide variety of populations and demonstrated good psychometric properties (Plummer et al., 2016; Wittkampf et al., 2007).

2.3 | Statistical analyses

All statistical analyses were performed using the R statistical programming language (R Core Team, 2020). We used the psychonetrics R package (Epskamp, 2020) for network models. Network plots were drawn using the qgraph package (Epskamp et al., 2012). Node placement for the admission network was accomplished using the Fruchterman-Rheingold method (Fruchterman & Reingold, 1991), which places nodes with stronger associations closer to each other. To facilitate interpretation, the obtained layout was also used for the discharge network. A list of all applied R packages can be found in the Supporting Information Material (Supplement B).

2.3.1 | Aim 1: Modeling an accurate MDD/anxiety symptoms network structure

Network analyses as well as latent variable models were performed using the R package psychonetrics (Epskamp, 2020). We estimated network models via the Graphical Gaussian Model (GGM; Epskamp et al., 2016) using maximum likelihood (ML) estimation. We removed nonsignificant parameters using Bonferroni-corrected significance levels of 0.05. Next, a forward-search strategy was used by adding back

TABLE 1 Description of sociodemographic and clinical characteristics of the sample ($N = 5614$)

Variable	Mean (SD) or *N* (%)
Age, years	42.24 (14.38)
Female	3570 (63.59%)
School diplomas	
High school	1728 (32.29%)
Secondary school	2012 (57.60%)
Still in school	178 (4.17%)
Unknown/unclear	132 (2.77%)
Did not finish school	105 (2.40%)
Special education	28 (0.78%)
Marital status	
Married/partnered	2397 (46.10%)
Unmarried	2109 (40.56%)
Divorced	573 (11.02%)
Widowed	120 (2.31%)
Treatment duration (days)	47.64 (15.81)
Primary diagnosis	
MDD, recurrent, moderate	1935 (34.47%)
MDD, recurrent, severe without psychotic features	976 (17.39%)
MDD, single episode, moderate	941 (16.76%)
Agoraphobia with panic disorder	585 (10.42%)
MDD, single episode, severe without psychotic features	379 (6.75%)
Social phobia	333 (5.93%)
Generalized anxiety disorder	71 (1.26%)
Specific (isolated) phobias	46 (0.82%)
MDD, recurrent, mild	35 (0.65%)
Agoraphobia, unspecified	25 (0.45%)
MDD, recurrent, severe with psychotic symptoms	11 (0.20%)
MDD, single episode, mild	11 (0.20%)
MDD, single episode, severe with psychotic features	11 (0.20%)
Other mixed anxiety disorders	8 (0.14%)
Other phobic anxiety disorders	7 (0.11%)
Anxiety disorder, unspecified	5 (0.09%)
MDD, recurrent, in remission	2 (0.04%)
Anxiety and depressive disorder, mixed	2 (0.04%)
Phobic disorder, not otherwise specified	1 (0.02%)
Recurrent, unspecified	1 (0.02%)
Other recurrent depressive disorders	1 (0.02%)
Other depressive episodes	1 (0.02%)
Secondary diagnosis	
Phobic anxiety disorders	4078
MDD, recurrent	3615
Other anxiety disorders	2220
MDD, single episode	2017
Somatoform disorders	1632
Eating disorders	635
Specific personality disorders	558
Persistent mood disorders	422
Reaction to severe stress and adjustment disorders	392
Hyperkinetic disorders	260

Abbreviation: MDD, major depressive disorder.
Note: Patients had one primary diagnosis but could have multiple secondary diagnoses.
Due to brevity, the ten most frequent two-digit ICD codes are used to summarize secondary diagnoses. A more detailed description of all diagnoses is offered in the Supporting Information Material (Supplement A).

parameters starting with those that show the largest modification indices. Parameter search was stopped when the Bayesian Information Criterion could not be further reduced (see Williams et al., 2019 for a detailed explanation of forward-search). We computed the strength and expected influence to determine node centrality. Strength is the sum of absolute edge weights of one node. Expected influence is simply the sum of all edge weights while keeping their signs. Since the GAD-7 was developed as a diagnostic tool for GAD, we performed a robustness check by repeating this analysis on a subsample ($N = 596$) that included only patients with diagnoses of both a depressive disorder and GAD (F41.1). We compared the similarity of this network with the model that includes the whole data set.

To estimate the stability of the estimated edges, we used non-parametric bootstrapping procedures. Stability of strength, expected influence, and their respective bridge variants were assessed using case-dropping bootstraps. In this procedure, varying proportions of the sample ranging from 10% to 75% are dropped and network models are estimated using only the remaining fraction of the data. Correlations of the bootstrapped measure between the subset models and the original are calculated. This way, the robustness of estimated parameters can be assessed. This procedure was also used to test for significant differences between centrality indices (Epskamp et al., 2017). Bootstrapping procedures were conducted with 1000 runs.

Network models at admission and discharge were compared using the network comparison test (NCT; van Borkulo et al., 2017). The NCT is a permutation-based hypothesis test for invariance of network structure, global strength of connections, and edge estimates. Since 120 edges are tested for invariance simultaneously, we corrected the alpha values for multiple comparisons using the method proposed by Holm (1979).

2.3.2 | Aim 2: Analysis of bridges between MDD and anxiety symptoms

Conventional measures of node centrality do not take into account community membership. Recently, Jones et al. (2019) proposed

bridge centrality as a way to control community membership. We computed bridge expected influence (BEI) to find the items that have the strongest connection to the other community. Similar to expected influence, BEI is calculated by summing a node's edge weights, but only edges that connect nodes from one community with the other are counted. Tests for significant differences between individual nodes' BEI values will be conducted based on the bootstrap analysis.

2.3.3 | Aim 3: Proposal of an empirically derived community structure

We used the Clique Percolation Method for weighted networks (CPMw; Farkas et al., 2007; Palla et al., 2005) to identify communities of depressive and anxiety symptoms based on the estimated models. The method is implemented in the R package CliquePercolation (Lange, 2019b). CPM is especially useful for psychometric networks, as it allows nodes to belong to more than one community. This algorithm works by detecting the subgraphs of nodes that are fully connected (*k*-cliques). These cliques are defined as adjacent when they share all but one node. Adjacent cliques are grouped into communities. Two parameters have to be set for CPMw: the parameter *k* determines the minimum size of k-cliques. The intensity (*I*) determines how strongly a *k*-clique has to be connected to be included in a community. Using a permutation test, the optimal setting for these parameters can be found (Lange, 2019a, 2019b). We allowed *k* to vary between 3 and 6 and *I* between 0.01 and 0.40. This covers a broad range of possible scenarios for the community structure. Permutation tests were performed on the admission and discharge network.

3 | RESULTS

Item- and scale-level descriptive statistics are presented in Table 2. According to the original cutoff criteria for PHQ-9, the severity of depression was classified as "severe" in 1327 patients (23.64%), "moderately severe" in 1663 (29.62%), "moderate" in 1555 (27.70%), "mild" in 912 (16.25%) and "minimal to none" in 157 (2.80%). Regarding anxiety, the severity of anxiety was classified as "severe" in 2101 (37,42%) patients, "moderate" in 1930 (34.38%), "mild" in 1312 (23.37%), and "minimal to none" in 271 (4.83%).

The standardized mean differences of scale scores were $d = -0.991$ (95% confidence interval: −1.03; −.952) for the PHQ-9 and $d = -0.997$ (95% confidence interval: −1.036; −0.958) for the GAD-7. These values were corrected for the correlation between pre- and postassessments (Morris & DeShon, 2002). These correlations were $r = .548$ for the PHQ-9 and $r = .503$ for the GAD-7.

TABLE 2 Full item text, item shorts used in network plots, and descriptive statistics of the PHQ-9 and GAD-7 at admission and discharge ($N = 5614$)

		Admission			Discharge		
Scale/Item	Item short	Mean	SD	Median	Mean	SD	Median
Depression (PHQ-9)		14.88	5.57	15	9.63	5.68	9
Little interest or pleasure in doing things	Anhedonia	1.99	0.91	2	1.15	0.78	1
Feeling down, depressed, or hopeless	Sad mood	1.92	0.91	2	1.17	0.84	1
Trouble falling or staying asleep, or sleeping too much	Sleep	2.16	0.97	3	1.57	1.00	1
Feeling tired or having little energy	Energy	2.25	0.86	3	1.44	0.89	1
Poor appetite or overeating	Appetite	1.45	1.06	1	0.94	0.95	1
Feeling bad about yourself—or that you are a failure or have let yourself or your family down	Guilt	1.68	1.05	2	1.04	0.97	1
Trouble concentrating on things, such as reading the newspaper or watching television	Concentration	1.80	0.99	2	1.28	0.97	1
Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual?	Motor	1.08	0.98	1	0.68	0.83	0
Thoughts that you would be better off dead or of hurting yourself in some way?	Suicide	0.54	0.75	0	0.35	0.66	0
Anxiety (GAD-7)		12.46	4.65	13	7.84	4.75	7
Feeling nervous, anxious, or on edge	Nervous	2.22	0.84	2	1.58	0.87	1
Not being able to stop or control worrying	Control worry	1.91	0.95	2	1.15	0.89	1
Worrying too much about different things	Too much worry	1.98	0.91	2	1.29	0.89	1
Trouble relaxing	Relax	2.21	0.87	2	1.42	0.91	1
Being so restless that it's hard to sit still	Restless	1.24	1.01	1	0.82	0.87	1
Becoming easily annoyed or irritable	Irritable	1.40	0.94	1	0.76	0.79	1
Feeling afraid as if something awful might happen	Afraid	1.49	1.02	1	0.83	0.86	1

Note: Scale values are presented as sum scores, not mean scores. Scale from 0 (not at all) to 3 (nearly every day).

3.1 | Aim 1: Modeling an accurate MDD/anxiety symptoms network structure

3.1.1 | Network analysis

Network plots at admission and discharge are presented in Figure 1, centrality indices in Figure 2. In the admission network, 68 of 120 possible edges were set to zero after Bonferroni correction. 15 edges were added back during the forward-search procedure. At discharge, 68 edges were removed and 12 parameters were added back.

Node centrality values are shown in Figure 2. "Sad mood" was the most central symptom in both networks, indicating strong connections with other symptoms. Other highly central symptoms include "restless" and "trouble relaxing," as well as "too much worry" and "uncontrollable worry."

3.1.2 | Network stability

Nonparametric bootstraps indicated that the majority of edges were stable. Confidence intervals of edges with estimated weights above 0.056 at admission and 0.058 at discharge did not include zero. In the admission network, the median width of bootstrapped 95% confidence intervals around nonzero edges was 0.085 (range:

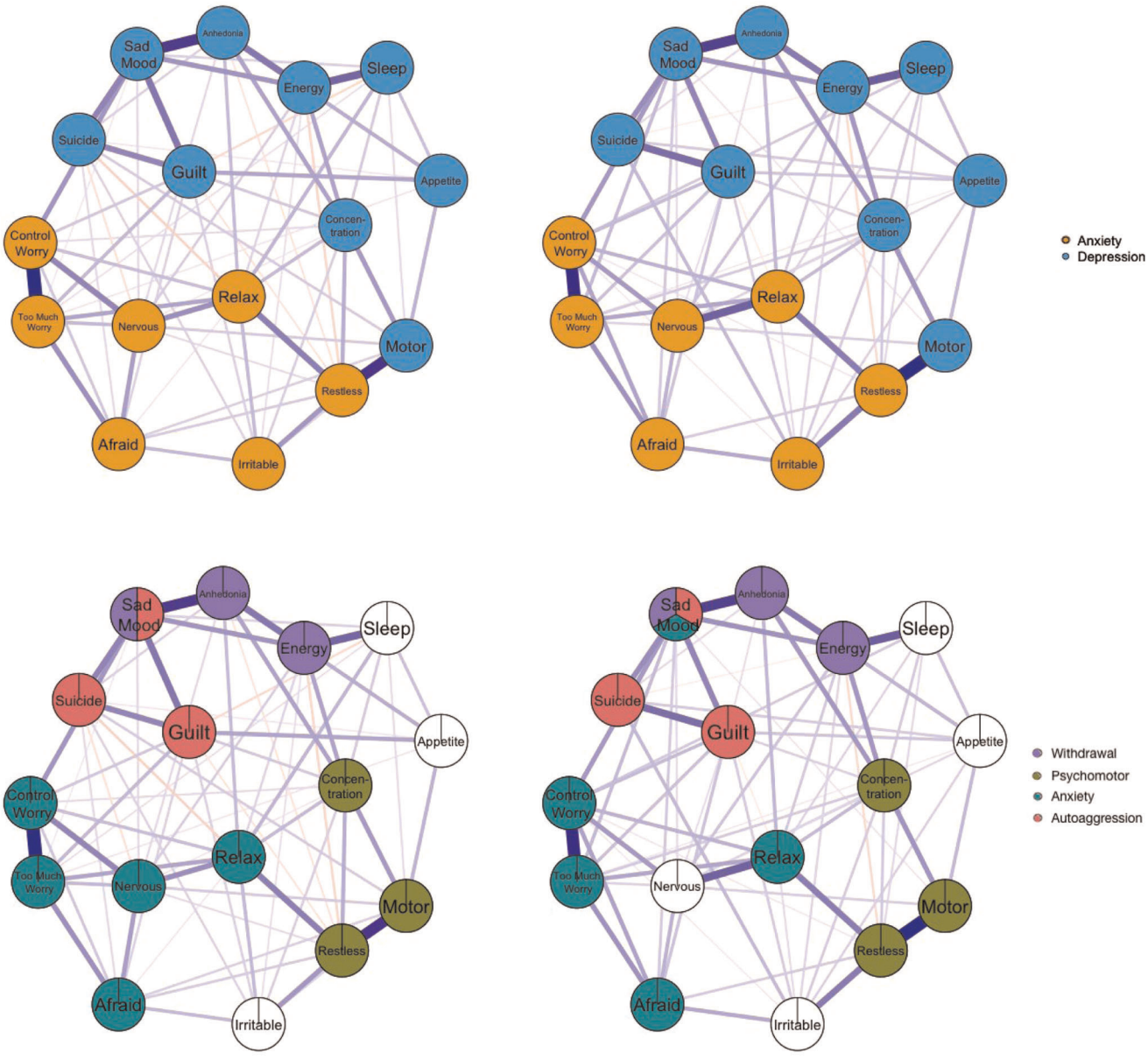

FIGURE 1 MDD/GAD symptom network at admission (top left) and discharge (top right) after removing and adding back edges. Nodes are colored according to their scale membership. Network graphs with nodes colored according to the empirically derived community structure are shown in the two bottom graphs. Nodes with multiple colors belong to multiple communities, while white nodes were not assigned to any community. Blue edges represent positive associations, red edges negative associations

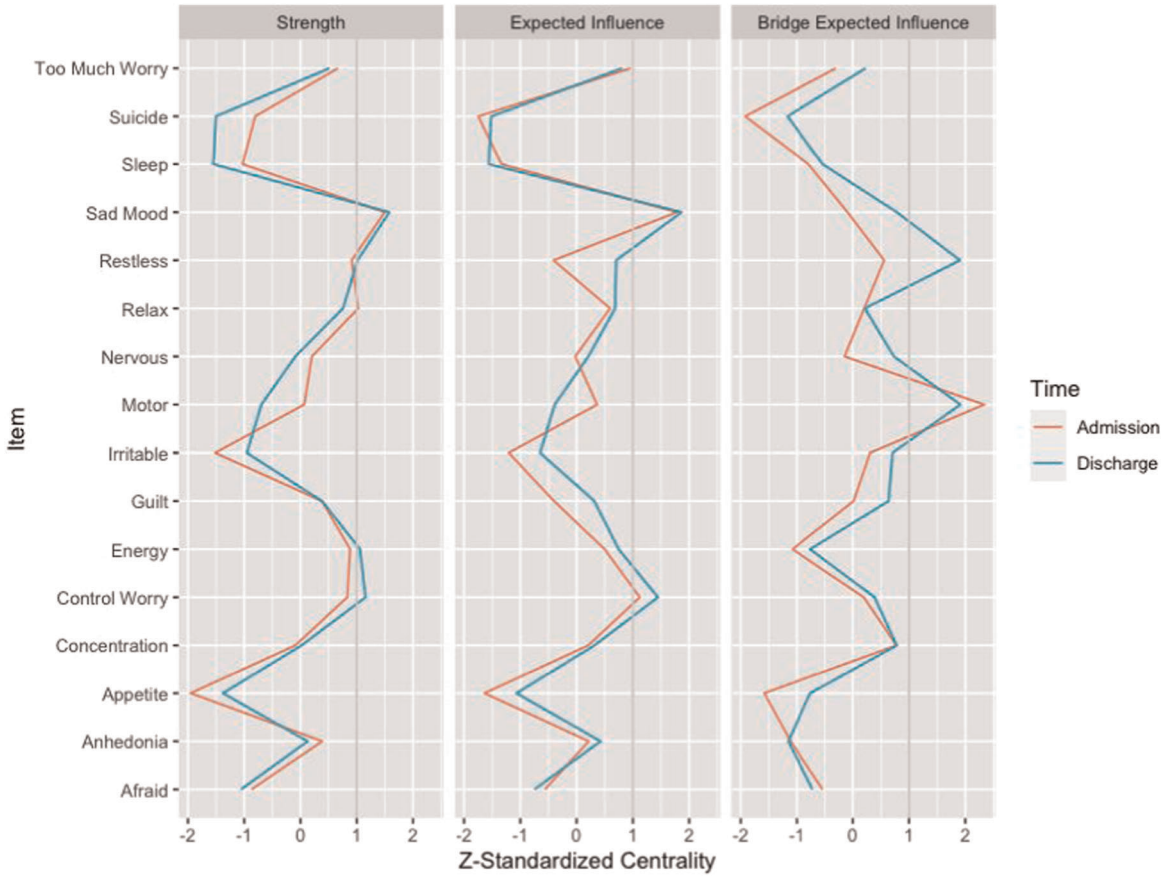

FIGURE 2 Strength, expected influence, and bridge expected influence at admission (red line) and discharge (blue line). All measures are Z-standardized

0.064–0.118). At discharge, stability decreased only slightly: the median width of CIs was 0.095 (range 0.063–0.132). Edges of network models estimated using only a fraction of the sample still correlated highly with those from the original model, never dropping below a correlation of 0.90 in any of the runs. Centrality measures were also stable, with correlations dropping below 0.90 only after leaving out more than half of the sample. More detailed information on the results of network stability analyses can be found in the Supporting Information Material (Supplement C).

3.1.3 | Comparison of admission and discharge networks

The network comparison test indicated that the overall network structure was not invariant ($M = 0.069$, $p = .022$). Conversely, there was no significant change in the global strength of connections (global strength at admission: 7.40, at discharge: 7.31; $S = 0.085$, $p = .39$). After correction for multiple comparisons, only two edges were not invariant: the edge between "control worry" and "too much worry" was decreased by −0.058 at discharge, and the edge between "sad mood" and "too much worry" increased by 0.069 at discharge. The overall profile of centrality was stable: Spearman correlations between centrality measures at both time points were $\rho = 0.92$ ($p < .001$) for strength and $\rho = 0.91$ ($p < .001$) for expected influence. The most notable change in centrality was observed for "restlessness." For this item, both expected influence and bridge expected influence increased. This can be explained by an increase of the correlation with psychomotor agitation, but also because the negative associations with "guilt" and "anhedonia" were not present at discharge.

To explore whether changes in node centrality are related to changes in symptom means on the group level, we calculated differences between centrality values and mean symptom scores at admission and discharge. Then, we estimated Spearman correlations of those difference values. However, we found no significant correlation between changes in item means and changes in any centrality measure (all $|r| < .35$, all $p > .14$).

3.1.4 | Comparison with Beard et al. (2016)

We obtained covariance matrices and item means from the supplementary materials provided by Beard et al. (2016). EBICglasso regularization was applied to the covariance matrices to obtain a network structure close to that reported in the original study. At admission, the Spearman correlation between the edges obtained

using our data and those reported by Beard et al. (2016) was close to perfect (ρ = 0.967, $p < .001$), suggesting a very close replication of the admission network. Centrality indices at admission were also highly correlated: we found Spearman correlations of ρ = 0.956 for strength and ρ = 0.991 for expected influence, both $p < .001$.

At discharge, the correlation between edges was less pronounced but still high (ρ = 0.792, $p < .001$) while centralities were again strongly correlated with ρ = 0.874 for strength and 0.900 for expected influence, both $p < .001$.

We repeated the analysis using unregularized partial correlations. Here, edges were correlated moderately at admission (ρ = 0.702, $p < .001$) and discharge (ρ = 0.700, $p < .001$). Correlations between centrality measures were high with ρ = 0.829 for strength and ρ = .941 for expected influence at admission and 0.832 for strength and 0.826 for expected influence at discharge, all $p < .001$.

3.1.5 | Comparison to patients with only MDD and GAD

At admission, the Spearman correlation between the edges obtained for the whole sample with those obtained from the subsample containing only patients with both MDD and GAD diagnoses was ρ = 0.708. At discharge, this correlation increased to ρ = 0.790. Centrality indices at admission were highly correlated with Spearman correlations of ρ = 0.844 for strength and ρ = 0.953 for expected influence, both $p < .001$. These correlations remained high at discharge, with ρ = 0.865 for strength and ρ = 0.953 for expected influence. Bridge expected influences were correlated with ρ = 0.850 at admission and ρ = 0.853 at discharge, suggesting similar bridge nodes. A graphical depiction of this network, including the centrality plot, can be found in the Supporting Information Material (Supplement D).

3.2 | Aim 2. analysis of bridges between MDD and anxiety symptoms

Bridge expected influence differed strongly from nonbridge centrality measures (Figure 2). Bootstrap centrality comparison tests revealed that, at admission, the strongest bridge symptoms were "moving slowly/restless (Motor)." The bridge expected influence of this item was significantly higher than any other value. "Trouble concentrating," "trouble relaxing," "restless," and "irritable" were also significantly stronger bridges than other symptoms. "Suicidal ideation" and "poor appetite or overeating" had significantly weaker connections to anxiety symptoms than all other depressive symptoms.

3.3 | Aim 3: Proposal of an empirically derived community structure

The permutation test resulted in an optimal value of 3 for *k*, so the minimum clique size was two nodes. The optimal value of the intensity parameter *I* was 0.165. Clique percolation analysis resulted in four communities. The first community included the items "sad mood," "guilt," and "suicide". Because the content of the included items describes self-deprecation and self-harm, this community was called "autoaggression." The second community included "concentration," "motor," and "restless." Given the more somatic content of these items, we propose the title "psychomotor symptoms." Next, a community consisting of "nervous," "control worry," "too much worry," "relax," and "afraid" was found This includes items that describe anxious arousal, which is why this group was called "anxiety." Finally, a fourth community included "anhedonia," "sad mood," and "energy," which we summarized under the label "withdrawal." The items "sleep," "appetite," and "Irritable" were not included in any of the communities. The community structure remained largely constant for the discharge network. However, the item "nervous" was not included in the "anxiety" community anymore. "Sad mood" was additionally included in the "anxiety" community.

4 | DISCUSSION

In this study, we estimated a network structure of depression and anxiety symptoms in a large naturalistic psychosomatic sample. This study aimed to accurately map this network structure, to use the resulting model to uncover symptoms that may explain the comorbidity of anxiety disorders and depression and to compare the performance of these models with factor models.

We estimated an accurate network structure of MDD and anxiety symptoms. The accuracy is in parts attributable to the large sample size and possibly to the robustness of the findings reported by Beard et al. (2016). By focusing on patients that were diagnosed with both depressive and anxiety disorders, we limited the influence of unmeasured influences on the network structure. As shown by bootstrap analysis, centrality measures were highly robust as well. Additionally, we showed that the majority of edges were stable when comparing them between admission and discharge, challenging the assumption that treatment changes symptom structure on the group level. We could closely replicate the overall network structure and centrality values reported by Beard et al. (2016). However, our results regarding the comparison of admission and discharge networks differed. Despite the high statistical power achieved with large samples, we found no evidence for an increase of global edge strength after treatment. Similar to our findings on edge invariance, this challenges previous studies reporting an increase of intercorrelation of symptoms during treatment (Beard et al., 2016; Fried et al., 2016). One possible explanation could be the diminished effects of repeated assessment due to the relatively long period between admission at discharge: while the average treatment duration reported by Beard et al. (2016) was 8 days, patients in our sample were treated over an average of 48 days. This, however, is challenged by the fact that treatment effects were roughly equal and changes in centrality in our sample were unrelated to changes in item means. Another possibility is that, by limiting our sample to patients with

multiple diagnoses, it only contains patients with relatively high symptom burden. It could be that mean changes in symptoms are less related to changes in network structure in more severe samples. According to the network theory of mental disorders, changes in network structure should lead to more sustainable treatment effects. Indirectly, this interpretation is supported by observations of higher recidivism, for example, in depressed patients with comorbid anxiety (Andreescu et al., 2007).

The strongest bridge symptoms between depression and anxiety disorders identified in this study were predominantly physical. In terms of content, these symptoms describe restlessness and the inability to end this restlessness. On the other hand, suicidality and changes in appetite were unique to depression. Physical symptoms as the most important bridge symptoms are in line with previous research. For example, one study on physical activity in patients with either depression, anxiety, or concurrent diagnoses showed that patients with concurrent disorders were more physically active than patients with only depressive or anxiety disorders (Helgadóttir et al., 2015). Patients with both MDD and GAD diagnoses also show lower heart rate variability compared to patients with only one diagnosis (Kemp et al., 2012) which was explained by chronically high levels of anxious apprehension leading to a chronic withdrawal of the parasympathetic nervous system. Including physiological and behavioral measures in psychometric network, models could be an interesting approach, as it will tell us how accurately self-report scales describe directly observable pathological processes and help explain the role of these processes as bridges or community-stabilizing entities. Attempts have been made to include nonpsychometric measures, like inflammatory markers for depression (Fried et al., 2019). For anxiety and depression, heart rate variability as a biological marker or results from startle response tests (Ray et al., 2009; Vaidyanathan et al., 2014) could be a useful addition.

The community structure we found in the estimated networks suggests that co-occurring depression and anxiety disorders can be understood as a network of core problem areas, reflecting components of an internalizing disorder. The community including psychomotor symptoms contains symptoms from both scales, which shows that it also serves as a bridge between depression and anxiety in this community structure. This is in line with studies on alternative taxonomies of mental disorders like the "hierarchical taxonomy of psychopathology" (HiTOP) that find MDD and GAD symptoms to be highly correlated (Kotov et al., 2017). On the other hand, some items were not included in any community. Due to the small number of nodes, the structure we found can only be considered preliminary. Further studies should examine communities in networks of more detailed inventories and test whether the four communities we found still occur.

Clinically, bridge symptoms, as well as communities, can be regarded as transdiagnostic, and interventions that target them are more likely to be effective for both disorders. There is some evidence that change in more central symptoms predict changes in other symptoms (e.g., Rodebaugh et al., 2018), which suggests that interventions focusing on the manipulation of psychomotor activity, like mindfulness-based approaches, relaxation exercises, or behavioral activation, should be highly effective especially in comorbid patients. Recent findings suggest stronger effects for behavioral activation when compared to acceptance and commitment therapy (Fernández-Rodríguez et al., 2020). However, it is still unclear whether interventions could target single symptoms (Bringmann & Eronen, 2018) and there is some evidence that current therapeutic interventions target multiple symptoms (Blanken et al., 2019; Boschloo et al., 2019). Including measures of relevant change processes (Santos et al., 2019) should be considered as a way to test symptom-specific change mechanisms theoretically implied by the intervention. Generally, caution is advised when drawing conclusions for clinical practice from cross-sectional network analyses.

Some limitations of this study need to be acknowledged. Our study relied only on self-report psychometric data for symptom assessment. Diagnoses based on structured clinical interviews were not available. Future studies should validate our findings using structured rating scales administered by clinicians that try to assess the same symptoms. It must also be critically noted that the scales used to cover only a subset of the symptoms relevant to DSM-5 diagnosis. The range of all possible symptoms is likely to be much larger. For example, Fried (2017) showed that the most common depression scales cover a total of 52 symptoms, none of which are covered by one single scale. Thus, we cannot exclude that other symptoms explain the comorbidity of anxiety and depression more accurately. Also, the PHQ-9 items measuring sleep problems, changes in appetite, and psychomotor agitation measure "absolute change." For example, high scores on the sleep problems item can mean either more or less sleep. The same is true for the item measuring psychomotor agitation and retardation. Interestingly, psychomotor agitation was strongly and positively correlated with restlessness in our sample, suggesting that at least in patients with comorbid anxiety and depression, the PHQ-9 item is more likely to be interpreted in the direction of agitation.

There was no detailed information on treatment courses of individual patients, so it is not possible to draw conclusions about the mechanisms of therapy. Also, because there was no control group, treatment-specific effects could not be analyzed. Including a treatment variable in network, models could lead to interesting insights, as demonstrated by Blanken et al. (2019).

In summary, in the accurate and robust network model presented here, physical symptoms are key to understanding depression with comorbid anxiety disorders. Future studies should try to explain this bridging function more precisely with suitable methods beyond psychometric questionnaires.

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CONFLICTS OF INTEREST

Dr. Brakemeier has nothing to disclose. Dr. Herzog has nothing to disclose. Dr. Kaiser has nothing to disclose. Prof. Voderholzer has nothing to disclose.

DATA AVAILABILITY STATEMENT

Data sharing does not apply to this article as only secondary analyses were performed on a routinely collected data set with permission to use for research purposes but without the explicit permission of data sharing by the patients.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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