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ORIGINAL ARTICLE

Network analysis of depression and anxiety symptom relationships in a psychiatric sample

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Background. Researchers have studied psychological disorders extensively from a common cause perspective, in which symptoms are treated as independent indicators of an underlying disease. In contrast, the causal systems perspective seeks to understand the importance of individual symptoms and symptom-to-symptom relationships. In the current study, we used network analysis to examine the relationships between and among depression and anxiety symptoms from the causal systems perspective.

Method. We utilized data from a large psychiatric sample at admission and discharge from a partial hospital program ($N = 1029$, mean treatment duration = 8 days). We investigated features of the depression/anxiety network including topology, network centrality, stability of the network at admission and discharge, as well as change in the network over the course of treatment.

Results. Individual symptoms of depression and anxiety were more related to other symptoms within each disorder than to symptoms between disorders. Sad mood and worry were among the most central symptoms in the network. The network structure was stable both at admission and between admission and discharge, although the overall strength of symptom relationships increased as symptom severity decreased over the course of treatment.

Conclusions. Examining depression and anxiety symptoms as dynamic systems may provide novel insights into the maintenance of these mental health problems.

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Introduction

Traditional conceptualizations of psychopathology presume that symptoms of mental disorders are reflective of underlying diseases. In this conceptualization, the co-occurrence or non-random clustering of symptoms is due to an underlying common cause (see Borsboom, 2008; Schmittmann *et al.* 2013). Thus, an entity such as major depressive disorder (MDD) is hypothesized to cause sad mood, anhedonia, and insomnia in the same way that the smallpox virus causes pustules, fever, and headache (Fried, 2015). The models employed to investigate psychopathology have assumed the common cause perspective of mental disorders. For example, reflective latent variable models of psychopathology, in which symptoms are indicators of an underlying latent variable, are consistent with a common cause perspective. Similarly, the use of sum scores to describe psychopathology severity assumes that symptoms are interchangeable indicators of the same underlying condition and can thus be summed to create a total score (see Fried & Nesse, 2015*a*, *b*).

Importantly, the common cause approach has the potential to obscure important differences between specific symptoms, as well as relationships among symptoms. For example, symptoms are differentially associated with impairments (Fried & Nesse, 2014), predisposing risk factors (Fried & Nesse, 2014) and neural substrates (e.g. Davidson *et al.* 2002; Kapur *et al.* 2012). Further, there is evidence that symptoms influence the development of other symptoms. For example, animal and human models suggest that

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restricted sleep is followed by depression and anxiety symptoms (e.g. Neckelmann *et al.* 2007; Novati *et al.* 2008; Baglioni *et al.* 2011), and hopelessness prospectively predicts suicidal ideation (e.g. Beck *et al.* 1990; Fawcett *et al.* 1990). Similarly, the alleviation of one symptom may positively affect other symptoms. In individuals receiving treatment for depression, changes in one symptom have been found to predict changes in other symptoms the following week, independent of a general decrease in symptom severity (Bringmann *et al.* 2015). One interpretation of this finding is that effective therapies target some symptoms first, which leads to downstream effects on other symptoms (Cramer *et al.* 2010). This interpretation directly conflicts with the common cause perspective. If symptoms directly interact, the assumption that the covariance among symptoms results from a common cause is not fully equipped to elucidate the structure of psychopathology.

The *causal systems perspective* (Borsboom, 2008) describes the possibility that symptom co-occurrence is due to direct symptom-to-symptom relationships rather than a common cause. According to this perspective, 'symptoms are constitutive of mental disorder, not reflective of it' (McNally *et al.* 2015, p. 2): in other words, 'causal, meaningful relationships between symptoms not only exist and should be acknowledged, but in fact are the very stuff of which mental disorders are made' (Borsboom & Cramer, 2013, p. 96). Thus, anhedonia, sad mood, and insomnia are not caused by an entity 'depression' in the same way that a brain tumor causes a headache. Rather, the causal systems perspective posits that symptoms directly influence each other and have their own genetic, neural, and psychological underpinnings.

Researchers have used network analysis to assess these symptom-symptom interactions. Network analysis, a set of procedures based on the modeling of dynamical systems (Barrat *et al.* 2012), provides a visual depiction of the complex associations among symptoms. A tightly connected network with many strong connections among symptoms is considered a 'riskier' network because activation of one symptom can quickly spread to other symptoms, leading to more chronic symptoms over time (van Borkulo *et al.* 2015). Network analysis also allows identification of highly 'central' or influential symptoms, defined by having, on average, strong connections with other symptoms. When a highly central symptom is activated (i.e. a person reports the presence of the symptom), it will influence other symptoms to become activated as well, maintaining the symptom network. Most relevant to the current study, recent work has supported the relative importance of sad mood and anhedonia in depression as these symptoms' centrality indices rank the highest among all depression symptoms (e.g. Fried *et al.* 2016*a*, *b*; Fried & Nesse, 2014). Interestingly though, together, the symptoms from the Diagnostic and Statistical Manual of Mental Disorders (DSM; APA, 2013) criteria for depression are not more central than non-DSM depression symptoms (e.g. sympathetic arousal) (Fried *et al.* 2016*a*, *b*).

The present study

To date, most network studies have examined symptom relationships and centrality within a single disorder. However, network analysis may be particularly useful for understanding co-morbidity because it permits the identification of potential pathways from one disorder to another (see Cramer *et al.* 2010). We sought to extend the existing literature in several ways by examining the symptom network of one of the most precarious diagnostic boundaries, i.e. between MDD and generalized anxiety disorder (GAD), in a large psychiatric sample. We utilized recent tools that have been developed to examine the stability of cross-sectional networks, as well as developed new procedures for this. We also used a clinical database with complete symptom data. This is crucial because the only other study that has examined MDD and GAD symptoms relied on an instrument that contained 'skip-out' criteria (Cramer *et al.* 2010). Thus, failure to endorse core symptoms (e.g. sad mood or anhedonia for depression) led to skipping all other symptoms of that disorder, resulting in large amounts of missing data. Finally, no studies have examined whether the MDD and GAD network changes over the course of treatment.

Thus, we designed the current study with three main goals: (1) characterize the MDD/GAD symptom network structure in a psychiatric sample, (2) determine the stability of the network, and (3) test whether the network changed over the course of treatment. For Aim 1, we investigated the connectedness between symptoms, the centrality of different symptoms, and identified potential symptoms that link disorders. Based on prior results (e.g. Bringmann *et al.* 2015; Fried *et al.* 2016*a*, *b*), we hypothesized that sad mood and anhedonia would exhibit high centrality among depression symptoms and that worry symptoms would be most central among anxiety symptoms. Similar to Cramer *et al.* (2010), we predicted that symptoms appearing in the diagnostic criteria of both MDD and GAD would serve as pathways between symptoms of anxiety and depression. In particular, we expected sleep (Fawcett *et al.* 1990; Durmer & Dinges, 2005; Ferentinos *et al.* 2009) and concentration (Davis & Nolen-Hoeksema, 2000; Joormann & Gotlib, 2008; Stefanopoulou *et al.* 2014) to link other symptoms of depression and anxiety symptoms. For Aim 2, given

our sample size, we expected the network edges representing the magnitude of association between symptoms and centrality indices to be stable. Finally, for Aim 3, we hypothesized that symptom networks created from data collected at pre- and post-treatment would have a stable structure. For example, a prior network analysis study showed that even as symptoms decreased overall, the most central symptoms remained the same (e.g. Robinaugh *et al.* 2014). At the same time, a recent study showed that the correlations among depression symptoms increased strongly and consistently over time while patients improved in symptomatology (Fried *et al.* 2016*a*, *b*). Thus, we hypothesized that the interconnectedness or global strength of symptom associations would increase over the course of treatment, even as the network structure (i.e. centrality of specific symptoms) remained stable.

Method

Participants and treatment setting

Participants were receiving treatment for mood, anxiety, personality, and psychotic disorders at the Behavioral Health Partial Hospital Program at McLean Hospital (for a review of the treatment, see Beard & Björgvinsson, 2013). Partial hospitals provide intensive treatment during the day with patients returning to their homes in the evening. The current study utilized self-report data collected in the routine clinical care of 1235 patients from July 2012 to July 2014 at admission and discharge. Missing data were handled with listwise deletion because typically participants were missing all items from one or both questionnaires. We excluded 206 subjects from admission data (final $N = 1029$) and 465 from discharge data (final $N = 807$; final N for both admission and discharge = 742). Data were collected using Research Electronic Data Capture (REDCap; Harris *et al.* 2009). Partners Healthcare Internal Review Board approved the study as exempt due to the use of a de-identified dataset.

Measures

The Mini International Neuropsychiatric Interview (MINI; Sheehan *et al.* 1998) was administered by doctoral practicum students and clinical psychology interns with weekly supervision by a postdoctoral fellow. The MINI is a structured interview to assess DSM-IV Axis I disorders. It has strong reliability and validity in relation to the Structured Clinical Interview for DSM-IV (kappas range from 0.89 to 1.0; Sheehan *et al.* 1998).

MDD and GAD symptoms were assessed via the Patient Health Questionnaire-9 (PHQ-9; Kroenke *et al.* 2001) and the 7-item Generalized Anxiety Disorder Scale (GAD-7; Spitzer *et al.* 2006), self-report measures of depression and anxiety symptom severity, respectively, over the prior 2 weeks. Participants rated symptoms on a scale from 0 (*not at all*) to 3 (*nearly every day*). Both PHQ-9 and GAD-7 have demonstrated good psychometric properties (Kroenke *et al.* 2001, 2007; Spitzer *et al.* 2006; Löwe *et al.* 2008) and have been validated as severity measures in our partial hospital population (Beard & Björgvinsson, 2014; Beard *et al.* 2016).

Analyses

Aim 1: Characterization of MDD/GAD symptoms network at admission.

Edges. In network parlance, symptoms are 'nodes,' and relationships between symptoms are 'edges.' To calculate the edges, we computed polychoric correlations between all items. Polychoric correlations estimate the association between two variables that are theorized to be continuous and normally distributed but are measured on ordinal scales. We estimated the network via a Graphical Gaussian Model (GGM; Lauritzen, 1996), in which edges represent conditional independence relationships among the nodes. These edges can be understood as partial correlations, representing the relationship between two nodes when controlling for all other relationships in the network. GGMs estimate a large number of parameters (i.e. 16 nodes requires the estimation of 136 parameters: 16 threshold parameters and $16 \times 15/2 = 120$ pairwise association parameters) that likely result in some false-positive edges. Therefore, it is common to *regularize* GGMs via the graphical lasso (glasso; see Tibshirani, 1996; Friedman, *et al.* 2008; for details). This algorithm shrinks all edges in the network, and sets small edges exactly to zero, which leads to a *sparse* (i.e. parsimonious) network that explains the covariance among nodes with as few edges as necessary. We estimated the GGMs using the R package qgraph (Epskamp *et al.* 2012) that automatically implements the glasso regularization in combination with extended Bayesian Information Criterion (EBIC) model selection as described by Foygel & Drton (2010). First, 100 different network models with different degrees of sparsity are estimated. Second, the model with the lowest EBIC is selected, given a certain value on the hyperparameter γ, which controls the trade-off between including false-positive edges and removing true edges. We set the starting value of γ to 0.5 as recommended by Foygel & Drton (2010). Detailed tutorials on network estimation, inference, stability, and regularization for psychopathological networks using the free statistical programming language R can be found elsewhere (Epskamp *et al.* 2016; Epskamp & Fried, 2016). For network visualization, the thickness

of the edges represents the magnitude of the association. Node placement was determined by the Fruchterman-Reingold algorithm, which places nodes with stronger average associations closer to the center of the graph (Fruchterman & Reingold, 1991). The R (R Core Team, 2014; version 3.2.3) package qgraph (version 1.3.3; Epskamp, *et al.* 2012; Friedman *et al.* 2014) was used to calculate and visualize the networks.

Centrality. We calculated several indices of node centrality to identify which symptoms are most central to the network (Opsahl *et al.* 2010). For each node, we calculated *strength* (absolute sum of edge weights connected to a node), *closeness* (average distance from the node to all other nodes in the network), and *betweenness* (the number of times that a node lies on the shortest path between two other nodes).

Aim 2: Stability of MDD/GAD network

We used two approaches to determine network stability, explained in detail in the Supplementary material. First, we used a permutation-based approach in which we divided the full sample (separately for both admission and discharge) into two randomly selected sub-samples, estimated networks independently, correlated edge and centrality values from the independent networks, and repeated this process 10 000 times.

Second, we used a bootstrap approach to calculate 95% confidence intervals (CIs) for the edge values (Epskamp *et al.* 2016). Because bootstrapped CIs could not be estimated for centrality values, we repeatedly correlated (*a*) centrality values calculated from the complete data set with (*b*) centrality values calculated from a subsample with a percentage (e.g. 20% or 50%) of nodes or participants missing. For the latter analysis, if correlation values decline substantially as nodes or participants are removed, we would consider this centrality metric to be unstable.

Aim 3: Comparing admission and discharge networks.

We examined two characteristics of the network that could change from admission to discharge: global network strength (i.e. change in the sum of all edges from admission to discharge) and network structure (e.g. if several of the most connected nodes at admission become some of the least connected at discharge and vice versa, it would indicate large structural change). We used a permutation test called the Network Comparison Test (NCT) to test for change in *global network strength* (van Borkulo *et al.* 2015). We investigated whether the observed difference between the absolute sum of all edges in each network was more extreme than the 95th percentile ($\alpha = 0.05$) on a null distribution. To make a distribution of NCT values under the null hypothesis that admission and discharge networks (i.e. dependent samples) are equal, we randomly switched, 50% of participants' admission and discharge data, constructed networks, calculated a NCT score and repeated this process 10 000 times.

To test for change in *network structure*, we correlated (*a*) the values for edges from the admission and discharge networks, and (*b*) the values for each centrality index (with Spearman rank-order correlations). We evaluated the stability of the network structure by examining the magnitude of the correlations rather than statistical significance. All analyses investigating changes of network global strength and structure included the 742 participants with complete data at both time points.

Results

Participants and overall treatment response

Patients were primarily single, White, and middle-aged (see Table 1). Table 2 presents mean scores for each symptom on the PHQ-9 and GAD-7. Paired-samples *t* tests, Bonferroni corrected for 18 tests, revealed that individual symptoms and total scores significantly decreased from admission to discharge ($p's < 0.001$; mean treatment duration = 8.2 days (S.D. = 3.2)).

Aim 1: Characterize MDD/GAD symptoms network at admission

Network structure

Fig. 1 presents the network at admission, and Fig. 2 presents the centrality indices. Approximately 38% of all network edges were set to zero. The two strongest edges were between '*too much worry*' and '*unable to control worry*' among anxiety items, and between '*sad mood*' and '*anhedonia*' among depression symptoms. Based on confidence intervals (see Supplementary material), both of these edges were significantly larger than all other edges. Within the anxiety items, '*unable to control worry*' had a strong connection with '*being nervous*', which had a strong connection with '*unable to relax*'. Among the ten (8.3%) strongest edges, only one linked anxiety and depression symptoms: '*motor*' from depression scale and '*restlessness*' from the anxiety scale. Although this cross-diagnostic connection makes this edge a candidate for a bridge symptom, '*motor*' (which does not distinguish between motor agitation and retardation) was on average more strongly related to anxiety items (average edge weight 0.051) than depression symptoms (average edge weight 0.036). All other PHQ-9 and GAD-7 items displayed higher connections with other items from the same questionnaire (average edge weight range 0.047–0.149) than across questionnaires (average edge weight

Table 1. *Demographic and clinical characteristics (n = 1029)*

Variable	Mean (S.D.) or *N* (%)
Age, years	35 (13.8)
Female	533 (52)
Education	
High school/GED or less	82 (8)
Some college	401 (39)
4-year college graduate	263 (26)
Post-college education	281 (27)
Marital status	
Never married/single	637 (62)
Separated/divorced/widowed	136 (13)
Married/living with partner	251 (25)
Race/ethnicity	
White	866 (84)
Asian	36 (4)
Multi-racial	39 (4)
Black/African American	23 (2)
American Indian or Alaskan Native	1 (<1)
Native Hawaiian or Pacific Islander	1 (<1)
Latino/a	17 (2)
Did not report	46 (4)
Primary diagnosis from medical chart (*n* = 1022)	
Schizophrenia	15 (2)
Schizoaffective disorder	29 (3)
Delusional disorder/unspecified psychosis	45 (4)
Major depressive disorder	
Without psychotic features	469 (46)
With psychotic features	47 (5)
Bipolar I disorder	105 (10)
Bipolar I with psychotic features	83 (8)
Bipolar II disorder	44 (4)
Mood disorder NOS	113 (11)
Anxiety disorder NOS	7 (1)
Depressive disorder NOS	8 (1)
Panic disorder	9 (1)
Generalized anxiety disorder	11 (1)
Social anxiety disorder	1 (<1)
Obsessive compulsive disorder	18 (2)
Post-traumatic stress disorder	16 (2)
Adjustment disorder	2 (<1)
Current clinical episode from MINI (*n* = 751)[a]	
Depressive episode	449 (60)
Manic episode	8 (1)
Hypomanic episode	4 (<1)
Mood disorder with psychotic features	31 (4)
Psychotic disorder	50 (7)
Panic disorder	143 (22)
Generalized anxiety disorder	170 (23)
Social anxiety disorder	211 (28)
Obsessive compulsive disorder	84 (11)
Post-traumatic stress disorder	95 (13)
Alcohol dependence	90 (12)
Alcohol abuse	41 (6)

GED, General equivalency diploma; NOS, not otherwise specified; MINI, Mini International Neuropsychiatric Interview.

[a] Percentages exceed 100% due to co-morbidity; 279 patients did not complete a structured interview while attending the partial hospital.

range 0.003–0.025). Finally, there were two other edges with CIs that did not contain zero and bridged anxiety and depression symptoms: '*guilt*' – '*too much worry*' and '*sad mood*' – '*nervous*'.

In the entire network, '*sad mood*' was the most central symptom across all centrality indices, followed by the anxiety symptoms: '*too much worry*', '*unable to control worry*', and '*unable to relax*'. Following these, the most central depression symptoms were '*low energy*', '*anhedonia*', and '*guilt/worthlessness*'. '*Suicide*' and '*irritable*' were the least central symptoms.

Aim 2: Stability of networks

For network *edges*, both the split-half permutation method (admission mean split-half $r_s = 0.75$, interquartile range 0.77–0.72) and bootstrap 95% CIs revealed high stability. Among *centrality indices*, strength was highly stable. Consistent with prior work (Epskamp *et al.* 2016), closeness and betweenness had relatively poor stability. These results were consistent across both admission and discharge (see Supplemental material).

Aim 3: Comparing admission and discharge networks

The repeated-measures NCT revealed that the *global edge strength* significantly increased from admission (NCT sum = 6.87) to discharge (NCT sum = 7.05; NCT difference = 18.51, $p = 0.007$). In other words, the sum of the absolute values of all edge weights was larger at discharge compared to admission. Regarding *network structure,* spearman correlations between admission and discharge were large for network edges ($r_s = 0.78$) and centrality indices [strength ($r_s = 0.96$), closeness, ($r_s = 0.60$), betweenness ($r_s = 0.71$)]. In combination, these findings suggest that the global connectivity of the network increased over time, but the structure of the network remained roughly intact.

Table 2. *Mean score for each symptom on the PHQ-9 and GAD-7 at admission and discharge*

	Mean rating	
	Admission	Discharge
Depression symptoms (PHQ-9)		
PHQ-1: Low interest or pleasure	1.79	1.26
PHQ-2: Feeling down, hopeless	1.90	1.31
PHQ-3: Trouble sleeping	1.86	1.20
PHQ-4: Tired or little energy	1.91	1.44
PHQ-5: Poor appetite/overeating	1.51	0.99
PHQ-6: Guilt	2.02	1.38
PHQ-7: Trouble concentrating	1.72	1.20
PHQ-8: Moving slowly/restless	0.84	0.50
PHQ-9: Suicidal thoughts	0.83	0.44
Anxiety symptoms (GAD-7)		
GAD-1: Nervous, anxious, on edge	1.97	1.44
GAD-2: Uncontrollable worry	1.77	1.17
GAD-3: Worry about different things	1.84	1.16
GAD-4: Trouble relaxing	1.81	1.12
GAD-5: Restless	1.08	0.71
GAD-6: Irritable	1.36	0.96
GAD-7: Afraid something awful might happen	1.26	0.73

PHQ-9, Patient Health Questionnaire-9 (Kroenke *et al.* 2001); GAD-7, 7-item Generalized Anxiety Disorder Scale (Spitzer *et al.* 2006).

Discussion

This study is the first to characterize depression and anxiety symptom networks within a large psychiatric sample, and with instruments that did not include skip-out criteria. Overall, the findings suggest that some symptom associations are stronger than others and that individual depression and anxiety symptoms are not equally important in the network. In general, connections between symptoms within each disorder were higher than connections between disorders. Importantly, both network edges and the strength centrality metric were stable, increasing confidence in drawing conclusions from the cross-sectional networks. In terms of change over the course of partial hospitalization, while symptom severity decreased and the strength of symptom associations increased from admission to discharge, the structure of the network remained stable.

The edges between '*too much worry*' and '*unable to control worry*' and between '*sad mood*' and '*anhedonia*' were significantly stronger than all other edges in the network. The motor symptom from MDD and the restlessness symptom from GAD were the most strongly connected items across the two disorders. Interestingly, the motor symptom from MDD showed stronger connections with anxiety symptoms than with MDD symptoms. Contrary to expectations, there was no strong bridge pathway involving sleep or concentration symptoms; however, unexpected bridge pathways emerged. Edges between '*guilt*' and '*too much worry*' and between '*sad mood*' and '*feeling nervous*' had confidence intervals that did not include zero. While our cross-sectional design does not permit inferences regarding the directionality of these bridge pathways, prior longitudinal data supports the possibility of a bi-directional connections such that anxiety can lead to depression (Kaufman & Charney, 2000; Wittchen *et al.* 2000; Avenevoli *et al.* 2001) and that depression leads to anxiety (Moffitt *et al.* 2007; Cramer *et al.* 2010; Zavos *et al.* 2012).

The strength centrality index (i.e. absolute sum of edge weights connected to a node) demonstrated excellent stability; thus, we focus our discussion of symptom centrality on strength. The symptoms of '*sad mood*' and '*too much worry*' were the most central to the network. These findings are consistent with their current status as hallmark symptoms required for a diagnosis of MDD and GAD and with prior studies (Fried & Nesse, 2014; Fried *et al.* 2016*a*, *b*). Low-energy was another highly central depression symptom; a finding that deviates from common conceptualizations of depression, but converges with another recent study that found that low energy was the most central depression symptom (Fried *et al.* 2016*a*, *b*). Finally, the least central symptom was suicidal ideation. Prior network analyses have yielded mixed findings regarding the centrality of suicidal ideation; although others have also found that is has low centrality (Fried *et al.* 2016*a*, *b*), other work suggested high centrality (e.g. Bringmann *et al.* 2015). In the current study, suicidal ideation had the lowest mean and standard deviation, which may have artificially lowered its centrality. It will be important for future studies to investigate how the frequency of specific symptoms affects their centrality.

We found that the strength of the relationships between the symptoms significantly increased from admission to discharge. This is consistent with recent work showing that the correlations among depression symptoms increase over the course of treatment (Fried *et al.* 2016*a*, *b*). These authors explored several possible explanations for changes in relationships across time, including spurious effects due to measurement flaws, but found no likely causes. For the current study, both admission and discharge sum scores were relatively normally distributed without any apparent strong floor or ceiling effects. There was a large shift from admission (50% of all responses were a 2 or 3 on the 0 to 3 scale) to discharge (28% of all responses

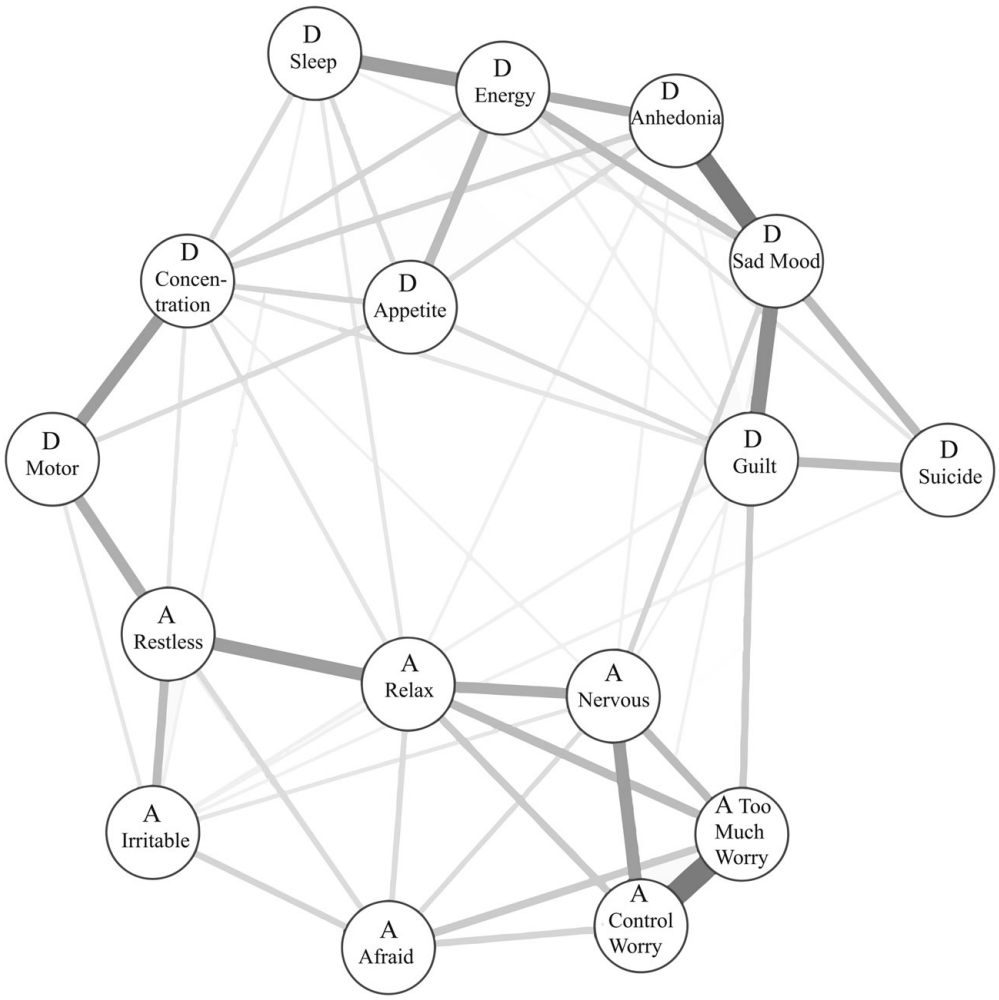

Fig. 1 - B/W online, B/W in print

Fig. 1. Network of anxiety and depression symptoms at admission.

were a 2 or 3), but we could find no relationship between this change in overall item endorsement and the increased correlations between the items at discharge. While the replication of this effect is intriguing, its cause it unclear. Additionally, as this study did not include a control group, it is not clear whether the increased global edge strength is due to treatment, repeated assessment, or some other factor. Despite the large reduction in symptom severity and increase in global strength of associations from admission to discharge, the edges between the symptoms and centrality values (i.e. the structure of the network) remained intact. Future research should test whether a network that retains its structure through treatment is more vulnerable to relapse, and whether interventions that successfully eliminate edges, thereby changing network structure, reduce vulnerability to relapse.

It is worthwhile to note that the main difference between examining MDD and GAD from a causal systems perspective *v.* a common cause perspective is conceptual rather than statistical in nature. Latent variable models can be transformed into network models and vice versa (Epskamp *et al.* in press; Molenaar, 2010). Instead, the two perspectives lead to different inquiries. If symptoms are indicators of an underlying cause, there is no theoretical basis to examine bridge symptoms between disorders; and, we know of no study using a common cause framework that has included such an analysis. Similarly, high factor loadings would suggest that some items are better indicators of the common cause than others; whereas, within a causal systems perspective, high centrality nodes in a network are interpreted as crucial in the etiology and maintenance of the network. The two perspectives also lead to divergent future directions. From the common cause perspective, future studies should explore the biological correlates of latent factors, such as the p-factor (Caspi *et al.* 2014). From the casual systems perspective, important next steps are testing whether, compared with lower centrality nodes, nodes

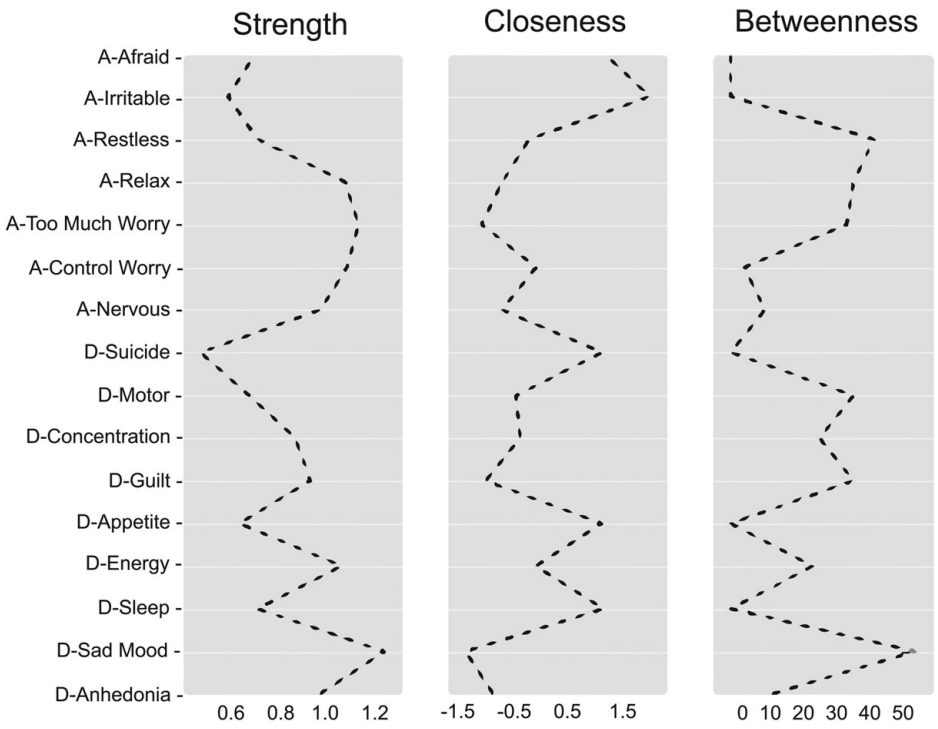

Fig. 2 - B/W online, B/W in print

Fig. 2. Centrality indices of network at admission.

with higher centrality are better prospective predictors of overall network activation (Robinaugh *et al.* 2016) and whether targeting more central nodes in treatment is more efficient and effective at reducing overall network activation compared with targeting peripheral nodes. Finally, it should be emphasized that these two conceptual frameworks are not mutually exclusive. There are likely to be some symptoms within a network that covary due to a common cause, which may itself be causally related to other symptoms.

There are several clinical implications of the current findings. As mentioned, interventions would likely be more efficient if they target central symptoms. Targeting the depression symptoms of sad mood, low energy, and anhedonia may therefore be most influential in reducing overall symptom severity. Cognitive Behavioral Therapy (CBT) targets most of these symptoms directly via behavioral activation and cognitive restructuring, which may explain the ability of very brief CBT to improve depression symptoms (e.g. Björgvinsson *et al.* 2014). Regarding anxiety symptoms, our findings suggest that treatments that first target worry should be most effective. However, CBT manuals (i.e. Craske & Barlow, 2006) for GAD do not target worry via problem solving and worry exposures until the end of treatment (chapters 8 and 10 respectively). The current findings suggest that targeting worry earlier should improve efficiency.

The current study had several strengths. First, unlike prior studies that used instruments with skip-out criteria (Cramer *et al.* 2010), all participants rated each symptom, resulting in more accurate network estimates. Second, data were collected as part of standard clinical care and therefore obtained from individuals who may not typically participate in research. Third, the sample had a range of DSM diagnoses and severity levels. Given that co-morbidity is more common than not, this sample provided a more realistic depiction of psychopathology than studies that screen out people with co-morbid disorders. Additionally, a diverse diagnostic clinical sample likely provides increased endorsement and variability among all symptoms, including symptoms outside of participants' diagnosed disorder(s), as compared to a general population sample, which may have a restricted range due to a large number of healthy individuals that endorse few or no symptoms.

The current study also had several limitations. First, the edges were calculated with cross-sectional data, precluding estimations of important network characteristics, such as the direction of edges or cyclical, self-reinforcing edges. Furthermore, cross-sectional edges represent both within- and between-subjects effects that cannot be disentangled (Hamaker, 2012). Experimental and prospective designs are required to test the assumptions underlying the causal systems perspective. Second,

although the qgraph glasso and EBIC procedure conducts model comparison that maximizes fit, we do not report any goodness-of-fit metrics for networks because they do not yet exist for this purpose (Kolaczyk & Csárdi, 2014). Third, we relied on self-report measures available from an existing database, and some items aggregated symptoms (e.g. combining insomnia and hypersomnia). Fourth, we used single-items to measure each symptom. This approach is crude (Fried & Nesse, 2015*a*, *b*) given that there are entire research areas on some nodes included here (e.g. anhedonia, Treadway & Zald, 2011). Furthermore, some nodes may actually be measuring overlapping constructs (e.g. '*too much worry*' and '*unable to control worry*'), which could artificially inflate edge weights and centrality. Currently, there is no canonical approach within networks to determine topological overlap (Zhang & Horvath, 2005) and combine overlapping items. Fifth, the sample was limited in ethno-racial diversity. Finally, a high degree of co-morbidity in our sample rendered subgroup analyses of 'pure' diagnostic categories (e.g. those with just MDD) impossible, though this limitation is offset by the greater ecological validity of a highly co-morbid sample.

In conclusion, consistent with the DSM, we found that anhedonia, sad mood, and worry were the most central symptoms of depression and anxiety. Although we found that anxiety and depression symptoms were more connected within-disorder than between-disorders, we identified a few potential edges bridging anxiety and depression. We also identified highly central items within each that would be prime candidates for future longitudinal and experimental research efforts to confirm their causal role and to identify their genetic, neurological, and cognitive underpinnings.

Supplementary material

The supplementary material for this article can be found at http://dx.doi.org/10.1017/S0033291716002300.

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Declaration of Interest

None.

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