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Clinical Interpretations of Symptom Networks Derived from Cross-Sectional Data: A Critical Re-evaluation

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Clinical Interpretations of Symptom Networks Derived from Cross-Sectional Data: A Critical Re-evaluation

By

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Ph.D., University of Houston, 2015

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An abstract of a thesis submitted to the faculty of the
James T. Laney School of Graduate Studies of Emory University
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Abstract

Clinical Interpretations of Symptom Networks Derived from Cross-Sectional Data: A Critical Re-evaluation

By Shabnam Hossein

The network approach to the study of psychopathology has gained significant interest among clinical psychologists in recent years; largely due to its potential to reveal the temporal dynamics among symptoms. This temporal inference has important implications for the conceptualization of mental disorders, the elucidation of potential "causal" relationships among symptoms, as well as the personalization of clinical interventions. Based on the type of data (longitudinal vs. cross-sectional), one can build directed or undirected symptom networks, both of which offer some degree of insight into the temporal dynamics of symptom relationships. While longitudinal data is preferable in this regard, most of the current literature used cross-sectional data to derive cross-sectional networks, and it is assumed that these networks are at least somewhat generalizable to temporal networks. Consequently, cross-sectional networks have frequently been used as the basis for suggesting that network analysis may help identify the best targets for intervention. The goal of this study was to assess the extent to which properties of symptom networks derived from cross-sectional datasets can be used to make inferences about symptom networks from longitudinal datasets. In study 1, we assessed effects of assumption violations related to the definitions of commonly used network centrality parameters in the psychopathology literature. Here, we used two publicly available cross-sectional datasets to compare different definitions of centrality. We find that depending on the type of network flow assumed in the definitions of centrality, different symptoms might be labeled as the most influential symptoms of the network. In Study 2, we used three separate longitudinal samples of individuals with varying degrees of depressive and anxiety symptoms to compare network properties between cross-sectional and temporal networks. We find that most features of temporal networks cannot be reliably measured based on cross-sectional methods, thereby challenging widely used conventions in the interpretation of cross-sectional symptom networks. Taken together, the results of these two studies suggest that greater caution is warranted in the interpretation of cross-sectional networks, and that more work needs to be done to empirically validate some of the methodological assumptions of the network approach.

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Introduction

In recent years psychopathology researchers have increasingly focused their attention on the interaction between symptoms of psychopathology in giving rise to mental disorders, rather than common causes (Borsboom & Cramer, 2013). This shift has been precipitated by the failure to identify common causes for any major mental disorder (Lilienfeld, 2014) after decades of research in the field of psychiatry. Interventions for the categories of mental disorders as identified by diagnostic manuals like DSM-5 and ICD-10 have enjoyed limited success (Lilienfeld, 2014), and co-occurrence of multiple mental disorders (comorbidity), as well as heterogeneity in the manifestation of a specific mental disorder remain as serious challenges to the common cause approach (Kessler et al., 1994; Monroe & Anderson, 2015).

One of the primary methods that has emerged for studying these symptom interactions among symptoms is network modeling drawn from graph theory (i.e. "the network approach") (Borsboom, 2017; Borsboom & Cramer, 2013). In this framework, symptoms of a mental disorder constitute the nodes of a complex network and the edges of the network are interpreted as interactions between those symptoms. Depending on the type of symptom data at hand, cross-sectional data or within-subject time-series data, the edges can be calculated from partial correlations between symptoms or lagged-regression among symptoms (Fried & Cramer, 2017). Importantly, the use of partial correlations has been proposed to give indications of potential causal pathways. Conditional independence relationships play a crucial role in causal inference. When all relevant variables are assumed to be observed, a partial correlation between variables A and B would only be expected to be non-zero if A causes B, B causes A, there is a reciprocal

relationship between A and B, or both A and B cause a third variable in the network (Epskamp & Fried, 2016; Koller & Friedman, 2009; Pearl, 2009). Because of this, partial correlation networks are thought of as indicative of potential causal effects. The network approach aspires to provide causal relationship between different symptoms and to utilize graph theory tools to analyze these symptom networks (Borsboom, 2017).

In recent years the network approach has been extensively applied to a variety of mental disorders, including, autism (Ruzzano, Borsboom, & Geurts, 2015), posttraumatic stress disorder (Armour, Fried, Deserno, Tsai, & Pietrzak, 2017; Birkeland, Blix, Solberg, & Heir, 2017; Fried et al., 2018; Greene, Gelkopf, Epskamp, & Fried, 2018; Knefel, Tran, & Lueger-Schuster, 2016; Mitchell et al., 2017), psychotic disorders (Isvoranu et al., 2017; Murphy, McBride, Fried, & Shevlin, n.d.; van Rooijen et al., 2017), major depression (Borkulo et al., 2015; Boschloo, Borkulo, Borsboom, & Schoevers, 2016; Fried et al., 2015; Hoorelbeke, Marchetti, De Schryver, & Koster, 2016; Madhoo & Levine, 2016; Santos, Fried, Asafu-Adjei, & Ruiz, 2017; Semino, Marksteiner, Brauchle, & Danay, 2017), eating disorders (Levinson et al., 2017; Olatunji, Levinson, & Calebs, 2018), obsessive compulsive and related disorders (Jones, Mair, Riemann, Mugno, & McNally, 2018; R. J. McNally, Mair, Mugno, & Riemann, 2017; Ruzzano et al., 2015), and anxiety disorders (Curtiss, Ito, Takebayashi, & Hofmann, 2017; Fisher, Reeves, Lawyer, Medaglia, & Rubel, 2017; Heeren & McNally, 2018).

A key focus of these studies has been to identify specific nodes (symptoms) that appear to have high centrality (i.e., greater connectedness with other symptoms) and to identify edges (connections) between symptoms that appear particularly strong. Highly central nodes (e.g. strength centrality, betweenness centrality, or closeness centrality) are

interpreted as being important for the etiology (Kossakowski et al., 2016), development, onset (Boschloo et al., 2016), progress, prognosis (Rhemtulla et al., 2016), remission(de Beurs, van Borkulo, & O'Connor, 2017), and recovery of mental disorders. Especially, they are suggested as targets for intervention (Armour et al., 2017; De Schryver, Vindevogel, Rasmussen, & Cramer, 2015; Deserno, Borsboom, Begeer, & Geurts, 2017; DuBois, Rodgers, Franko, Eddy, & Thomas, 2017; Fried et al., 2018; Knefel et al., 2016; Madhoo & Levine, 2016; Richard J. McNally et al., 2015; Mitchell et al., 2017; Robinaugh, Millner, & McNally, 2016; Semino et al., 2017; Sullivan, Smith, Lewis, & Jones, 2018; Werner, Štulhofer, Waldorp, & Jurin, 2018).

Importantly, however, while much of the purported value of the network approach is the study of symptom dynamics, the majority of papers using the network approach thus far have relied on constructing symptom networks from cross-sectional data. While this is not inherently problematic, the interpretations and conclusions offered from analysis of these cross-sectional networks frequently make claims about the implied temporal dynamics. I.e., the topology of these cross-sectional networks is assumed to provide meaningful information regarding the flow of influence between symptom nodes over time.

In the current paper, we evaluate two potential problems with this interpretation. The first is that the definitions of centrality commonly used in network studies make very explicit assumptions about how one node may influence another. While inter-relatedness among symptoms is often presented as being intuitive (a commonly used example is how insomnia leads to fatigue (Borsboom & Cramer, 2013; Hofmann, Curtiss, & McNally, 2016), the specific mechanisms for this influence remain poorly understood. Presumably,

symptoms influence each other through a variety of biological and contextual factors that may or may not be consistent across different symptom relationships (i.e., the mechanisms by which insomnia influences fatigue may be quite different than the mechanism by which anxiety influences fatigue). Consideration of the mechanisms of influence matters for cross sectional networks as it can determine the measure of centrality that is most appropriate (Borgatti, 2005). Currently, almost all studies make use of the Freeman definition of centrality (Freeman, 1978), which assumes that the symptom influence on other symptoms flows along the shortest path between two symptom nodes. This model makes sense when applied to situations involving physical transportation; e.g., a truck driver may seek to take the shortest path from point A to point B and intersections that frequently lie on the shortest path between two points will have high centrality in a network model of delivery routes. Such a model, does not work well for other forms of spreading influence, such as transmission of a viral infection or a rumor within a community of individuals. Indeed, there are many potential definitions of centrality that were derived from other fields such as computer science, social science, and physics (M. Newman, 2010), and the validity of their application to psychiatric symptoms has yet to be investigated empirically. Therefore, interpreting the importance of nodes based on a single, untested definition of centrality is potentially problematic.

A second problem is the implied assumption that the structure of a network derived from cross-sectional data would be similar to the structure of a network derived from time-series data collected in the same individuals, were such data available. This problem is particularly evident when the weights of the edges are interpreted in a dynamic context. It is implicitly assumed that the edges show at least partially causal

relationships through the symptoms *over time* (e.g. as in Afzali et al., 2017; Anker et al., 2017; Heeren, Jones, & McNally, 2018; Jones et al., 2018; Ruzzano et al., 2015); therefore, the higher the edge weight, the higher the probability that the activation of one symptom at one timepoint will cause another symptom to become activated at a later timepoint. In other words, it is assumed that topological properties of the symptom networks can be predictive of onset or prognosis of mental disorders (Borkulo et al., 2015; Murphy, McBride, Fried, & Shevlin, 2017; van Rooijen et al., 2017).

Here, we evaluate these two issues empirically using a collection of five independent datasets. To investigate the impact of different definitions of centrality, we compared the commonly used Freeman definition and two other commonly used definitions of centrality on two large datasets, and determine how the centrality ranks of the nodes change by changing the definition. The first was a “random walk” definition of centrality, which assumes that the influence of a symptom will spread in a random fashion until it reaches other symptoms. The second centrality measure used was a “communicability model” of centrality, which is similar to a random walk but takes into consideration the path lengths between nodes, thereby making it a hybrid of the Freeman and random walk approaches.

To investigate the second issue regarding the extent to which temporal networks could be inferred from cross-sectional networks, we compared within-sample temporal and cross-sectional networks constructed from three ecological momentary assessments (EMA) samples. A temporal network was fit for each of these time-series datasets using qgraph. Each time point of a time-series data is a cross-sectional window of data. The cross-sectional networks were fit for these time points, and were compared with the

temporal network based on different metrics such as edge weight comparisons and centrality measures comparisons.

Our aim in this paper is to provide an initial empirical evidence that these two issues, different definitions of centrality and temporal/causal interpretations of cross-sectional networks, carry important ramifications for psychopathology symptom networks. These are important challenges that need to be dealt with if symptom networks are to be a valid model for psychopathology.

Methods

Study 1

To investigate the impact of different definitions of centrality, we compared the widely used Freeman definition and two other commonly used definitions of centrality on two large cross-sectional datasets. We determined the Spearman correlation between the Freeman centrality indices and those of the other definitions of centrality, as well as how the change in the centrality definition re-ordered the centrality ranking of the nodes.

Data.

Sample 1.1. The first cross-sectional sample is obtained from (R. J. McNally et al., 2017), where the data from 408 patients treated between 30 July 2012 and 22 June 2015 in the residential and intensive out-patient units of the Obsessive–Compulsive Disorder Center at Rogers Memorial Hospital based in Oconomowoc, Wisconsin were used. These patients were assessed on their OCD and depressive symptoms upon admission by the Yale–Brown Obsessive Compulsive Scale – self-report (Y-BOCS-SR), and the Quick Inventory of Depressive Symptomatology – self-report version (QIDS-SR)

respectively. These 26 symptoms (10 symptoms of OCD and 16 depressive symptoms) constitute the nodes of the network model of this dataset.

Sample 1.2. The second cross-sectional sample is obtained from (Fried et al., 2018) where 526 traumatized patients data collected between 2001 and 2005 was studied. These patients were enrolled at a Dutch mental health center specializing in treatment of patients with severe psychopathology and a history of complex trauma. All patients were assessed with the Harvard Trauma Questionnaire (HTQ), as part of the routine diagnostic procedure. The 16 PTSD symptoms as measured by HTQ constitute the nodes of the network model of this dataset.

Network Flow and Analysis. The default definitions of betweenness centrality and closeness centrality used in the psychopathology networks literature, that is also implemented in the qgraph package (Sacha Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012), is the Freeman "shortest path betweenness" definition of these indices, as defined by equation 1 (Freeman, 1978; Opsahl, Agneessens, & Skvoretz, 2010):

$$B_F(v) = \sum_{s,t \in V} \frac{\sigma(s,t|v)}{\sigma(s,t)} \qquad \text{Eq. 1}$$

where $\sigma(s,t)$ is the number of shortest (s,t)-paths, and $\sigma(s,t|v)$ is the number of those passing through node v. This definition of betweenness centrality implies that the influence of one symptom on another flows along the "shortest path" between two nodes. It is conceptually unclear, however, what the precise definition of a "path" in this context would be. Moreover, there are many alternative models of inter-symptom influence that could be used For instance, one can define a typology of network flows based on two dimensions of the kinds of trajectories that information may follow (geodesics, paths,

trails, or walks) and the method of spread (broadcast, serial replication, or transfer)(Borgatti, 2005).

Study 1 Data Preparation and Network Modeling. To show the effects of assumptions regarding the information flow on the centrality of nodes, we considered two other commonly used centrality indices in the social network literature (Estrada, 2016; M. E. J. Newman, 2005): random-walk betweenness (RWB) and communicability betweenness (CB). The RWB of a node *v* is equal to the number of times that a random walk starting at *s* and ending at *t* passes through *v* along the way, averaged over all *s* and *t*. The CB is based on all walks connecting two nodes *s* and *t* that pass through *v* weighted by path length; in other words, it is a betweenness centrality that accounts for the shortest path connecting two nodes, but also acknowledges the existence of other (non-shortest) paths, giving them less significance. The Freeman centralities were calculated using qgraph (Sacha Epskamp et al., 2012), the common R package used in the symptoms network literature, and the other definitions of centrality were calculated using NetworkX (Hagberg, Schult, & Swart, 2008) package in Python.

To compare the resulting centrality parameters derived from these different definitions of centrality, we calculated the Spearman correlation between the Freeman centrality ranks and those of the RWB and CB, as well as the changes in the centrality ranks of the nodes when different definitions are applied.

Study 2

To investigate the extent to which temporal networks could be inferred from cross-sectional networks, we compared within-sample temporal and cross-sectional

networks constructed from three ecological momentary assessments (EMA) samples. A temporal network was fit for each of these time-series datasets using the package mlVAR (Epskamp, Deserno, & Bringmann, 2016). The cross-sectional networks were fit for each of time points of a dataset, and were compared with the temporal network of that dataset on different metrics such as edge weight comparisons and centrality measures comparisons.

Data.

Sample 2.1. The first time-series sample (sample 2.1) is from an ongoing experiential sampling research study at Emory University.

Participants. The participants in this study were adults between the ages of 18 and 65 years who were fluent in English. People with a history of psychosis, bipolar disorder, manic episodes, or frequent users of recreational drugs or other mind-altering substances as assessed by self-report were excluded from the study. Participants were recruited from both the Emory University student population and surrounding community through posters distributed on the Emory University campus and online advertisements.

Procedure. Prior to the first visit, all participants completed an online screening questionnaire to assess initial eligibility. Participants meeting eligibility criteria described above were then invited to the lab for a baseline session consisting of self-report measures, computer tasks, and instructions for the EMA portion of the study. After the baseline session participants received text messages containing hyperlinks to the surveys they filled out six times a day, every other day for four weeks (total of 90 time points). At the baseline session, the 12-hour period that was convenient for each participant to receive the text messages was asked. The messages were scheduled to be delivered every

two hours in that period. The surveys contain items assessing the positive and negative affect, depressive and anxiety symptoms, and predicted and actual enjoyment of their 2-hourly activities. All study procedures were approved by the Institutional Review Board of Emory University, and all participants provided written informed consent.

Sample 2.2. The second time-series sample (sample 2.2) is obtained from a previously published randomized controlled trial conducted in the Netherlands (Geschwind, Peeters, Drukker, van Os, & Wichers, 2011). The study followed 130 participants with residual symptoms of depression after at least one episode of Major Depressive Disorder (MDD) for 12 days. The first six consecutive days were the baseline period, and the second six days were the treatment period in which the participant would be randomly assigned to treatment or control group. Here, we used the data for the baseline period. During this period, the participants were randomly notified by a beeper in each of the ten 90-minute time blocks from 7:30 AM to 10:30 PM (total of 60 time points). When notified, participants were instructed to fill out self-assessment forms, collecting reports of their current mood and context within 15 minutes. All self-assessments were rated on 7-point Likert scales. The items we used for analysis here are the ones that were used (and thus the data was available for) by (Bringmann et al., 2013): positive mood items including cheerful and relaxed, negative mood items including fearful and sad, an emotion regulation item, worry, and the pleasantness of the event (the pleasantness of the most important event that happened between the current and the previous response).

Sample 2.3. The third time-series sample (sample 2.3) is from a previously published personalized psychotherapy study at the University of California, Berkeley

(Fisher & Boswell, 2016; Fisher et al., 2017). These data are part of an ongoing, multiphase study in which participants with primary diagnosis of Generalized Anxiety Disorder (GAD) or MDD complete repeated measure assessments four times a day for at least 30 days before the therapy phase (total of 120). Participant's standard waking time and their preferred time window was inquired at first. This window was split into four equal blocks of three hours, and the participants were notified at a random time within each block (with the additional constraint that surveys should be given at least 30 minutes apart) to fill out the survey.

Surveys contained the extant symptoms of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for GAD and MDD, as well as additional items gauging positive affect, negative affect, rumination, behavioral avoidance, and reassurance seeking. Participants rated their experience of each item over the preceding hours using a 0–100 visual analog slider. Here, from the 21 items answered on the experience sampling surveys, we used seven of these variables related to positive and negative affect and depressive and anxiety symptoms. Given that we wanted to study the nomothetic cross-sectional and temporal network, reduction of the number of variables was necessary in order to avoid constructing empty regularized networks. Also, in accordance with the type of items assessed in the other two studies, here we chose the items assessing mood as well.

Study 2 Data Preparation and Network Modeling. For all the three time-series datasets, we excluded the missing data for each participant and assumed that the missing time points did not exist. Then, for each of the samples we created a dataset containing the time-series data of all the participants over the period of the data collection, and series

of cross-sectional datasets for each time point of that period. For instance, sample 2**.**2 has one dataset containing the time-series data of all the participants, which was used to create the population temporal network. Sample 2**.**2 also had 60 datasets assigned to it for each of the time points that the participants filled out the surveys. These were used to generate 60 cross-sectional networks. In sample 2**.**3 we only choose the first 108 time points to generate the cross-sectional networks. This was done to make sure that in all of the cross-sectional datasets there are at least 30 responses. In sample 2**.**1, 70 time points were chosen to make sure that in all of the data points there are at least 50 responses. The temporal (lag-1 regression model) and the cross-sectional networks were generated using the *q-graph* and *mlVAR* packages in R.

For each of the time-series samples (sample 2.1, sample 2.2, and sample 2.3) the cross-sectional networks were compared with each other and also with their corresponding temporal network. The metrics that were used to compare these networks are as follows.

Network Comparison Metrics. Based on our review of prior network papers, we identified the following set of topological/structural metrics that seemed most relevant to determining the extent to which temporal network characteristics may be recovered from cross sectional networks.

Edge Comparisons. In order to compare the edges of the cross-sectional networks we looked at the percentage of the total edges that change sign in different cross-sectional networks (Sign Change). This does not include the edges that have non-positive or non-negative weights throughout different time points. Also, we calculated the number of times an edge that is present in the temporal network is also present in the cross-sectional

networks (Edges: Present), and the number of times that an edge that is not present in the temporal network is also not present in the cross-sectional networks (Edges: Not Present). The percentage of the time that the top 6 edges of a cross-sectional network with the highest edge weights are the same as the top 6 edges of the corresponding temporal network was also calculated (Top 6 Edges).

The correlation between edge weights of a cross-sectional network and that of the temporal network was also computed. This was done for all the cross-sectional networks of each sample. It should be noted that when comparing temporal networks and cross-sectional network, the temporal networks were treated as undirected. In other words, the corresponding elements of the adjacency matrices were compared with each other except for the self-loops on the diagonal. Additionally, for some of the time points the networks were empty (due to the balance between sensitivity and specifity; gamma=0.5) and all the edges were zero. Those networks were excluded when calculating the correlations. In the case of sample 2.3, gamma of 0.5 resulted in lots of empty cross-sectional networks; therefore, we set gamma to 0.35.

Centrality Measures. Freeman Betweenness and Closeness were computed and compared for the temporal network and cross-sectional networks of each sample. Degree centrality, another common centrality, was not used here for comparison because in the directed temporal networks we are dealing with in-degrees and out-degrees, whereas in undirected cross-sectional networks one can only talk about degree of each node. This makes the comparison incommensurable.

"Out of Sample" Comparisons. The comparisons described above are based on similar subjects for temporal and cross-sectional networks. In practice however, results

from a sample are assumed to be generalizable to other samples of individuals (i.e., random effects). To assess generalizability of cross-sectional networks to a temporal network constructed from a *different* set of individuals, we divided sample 2.2 (the largest sample) into two samples (first 60 participants in one group and the other 60 participants in another). We calculated 60 cross-sectional networks (for each of the 60 time points) for the first group, and a temporal network for the other group. The cross-sectional networks and the temporal network were then compared based on the same comparison metrics described above. We denote this sample as sample 2.2 (out of sample) in the figures and tables, as compared to sample 2.1 (in sample).

Results

Study 1

Centrality Rank Order Correlations Across Distinct Centrality Definitions.

To demonstrate the importance of considering the appropriate metric of centrality, we examined spearman correlations of symptom centrality ranks when centrality was estimated using Freeman Betweenness (FB), Randwom Walk Betweenness (RWB) or Communicability Betweeness (CB). We predicted that if the definition of centrality is immaterial to the assessment of centrality, then the rank-order correlations across these different centrality definitions should be very high. For sample 1.1, correlations between FB and RWB and FB and CB were (spearman r = 0.82, p = 3.09e-07) and (spearman r = 0.35, p = 0.08), respectively (See Figure 4A). For sample 1.2, correlations between FB and RWB and FB and CB were (spearman r = 0.81, p = 0.0001) and (spearman r = 0.31, p = 0.23) respectively (See Figure 4B).

Change in Centrality Rank Across Distinct Centrality Definitions.

As an additional comparison, we also identified the change in centrality rank for each node when moving from FB to either RWB or CB (Figure 4). For instance, this analysis revealed that the betweenness centrality ranks of the nodes could change up to 15 ranks in sample 1.1 ranks depending on the definition.

Study 2

The focus of study 2 was to assess the extent to which network configuration (e.g., edges, present and not present) as well as centrality measures constructed from cross-sectional data were representative of the temporal networks derived from the same sample of individuals. To this end, we compared temporal and cross-sectional networks constructed from three EMA samples. Visual depictions of the temporal network and "average cross-sectional network" for each of the samples 2.1, 2.2, and 2.3 are presented in Figure 1. Since there are 70, 60, and 108 cross-sectional networks associated with each of the samples, we only showed the "average cross-sectional network" for each of the samples, defined as the network where its adjacency matrix is the average of the all of the cross-sectional networks' matrices.

Edge weight correlations between temporal and cross-sectional networks.

To assess the extent to which the edge weights of a given cross-sectional network correlated with the associated temporal networks, we first evaluated pearson correlations for each of the three samples. As shown in Table 1, the correlation between the edges of the cross-sectional networks and the temporal networks range from 0.42 to 0.73 (p-values

ranging from 2.3e-11 to 0.46) across the three samples suggesting moderate agreement between the edge weights (Figure 2).

Proportion of edges present/not present across temporal and cross-sectional networks.

The average proportion of the time that an edge was present in a cross-sectional network when the same edge was present in the corresponding temporal network was 0.79 across the three samples, suggesting strong overall agreement between cross-sectional and temporal estimates of edges present. In contrast, the proportion of the time that an edge was not present in the cross-sectional network when the same edge was not present in the temporal network was only 0.46, suggesting much greater disparity between temporal and cross-sectional networks in terms of edges estimated as not being present.

Sign Change.

Averaging over all the three samples, 57.3% of edges change sign (i.e., positive or negative correlation) in at least one of the cross-sectional networks of that sample. This means that more than half of the edges that one might find at one cross-sectional window of time, might not even have the same sign in another window of time.

Top 6 Edges.

Averaging over all the three samples, only 16.97% of the cross-sectional networks have the same top 6 edges as of the corresponding temporal network. This shows a great disparity between the most influential pathways suggested by cross-sectional networks compared to ones offered by temporal networks.

Centrality comparisons.

Figure 3 shows the comparison between the temporal network and the average cross-sectional network in closeness and betweenness centrality indices for each of the three samples.

"Out-of-sample" Network Comparisons.

To assess the generalizability of cross-sectional networks to a temporal network derived from a distinct set of individuals, one of the samples was divided into two subsets. As shown in Table 1, the average correlation between the edges of a cross-sectional network and the temporal network is 0.42 (p-values ranging from 2.8e-5 to 0.29) in this sample. The proportion of the time that an edge was present in a cross-sectional network when the same edge was present in the temporal network was 0.80, whereas, the proportion of the time that an edge was not present in the cross-sectional network when the same edge was not present in the temporal network was only 0.31. 66.7% of edges changed sign in at least one of the cross-sectional networks of this sample, and 15% the cross-sectional networks had similar top 6 edges. The results of all the metrics suggest much greater disparity between temporal and cross-sectional

networks when generalizing cross-sectional networks to out of sample temporal networks.

Discussion

In this paper, we examined a critical assumption underlying the conceptual appeal of network approaches to the study of psychopathology: the potential for inferring causal dynamics between symptoms (Borsboom, 2017; Borsboom & Cramer, 2013). Because of its ability to measure inter-symptom relationships, the network approach has generated substantial interest among the clinical researchers, and the number of papers applying this method has proliferated in recent years. While we agree that the network approach warrants further study, we suggest more empirical work needs to be done to validate the common interpretations of network analyses, particularly those based exclusively on cross-sectional data sets. Indeed, we feel that there has been a certain degree of hastiness in the extent to which theoretically plausible ideas regarding the significance of a symptom network have become widely accepted as fact. The tendency to claim clinically relevant applications for network models is potentially premature, and may ultimately delay the widespread adoption of the network approach. We therefore suggest that more empirical studies designed to explicitly assess the core assumptions underlying the network approach are needed. Specifically, researchers need to empirically study the appropriateness of the graph theory tools advocated by the network approach in the context of psychopathology.

Here we addressed two such common assumptions used in the psychopathology network literature. Study 1 focused on assumptions underlying the definition of centrality

measures, a set metrics derived from graph theory that have been particularly widely-used in the psychopathology network literature (de Beurs et al., 2017; Richard J. McNally et al., 2015; Robinaugh et al., 2016). Centrality measures are applied to network models as a means of quantitatively defining the relative contribution of different network nodes, so as to identify the most "influential" nodes. Depending on the context and the properties of the node interactions (information flow), different definitions of centrality should be used. However, in the psychopathology network literature the two most commonly used centrality indices (betweenness centrality and closeness centrality) are defined in terms of the shortest path on the network without any justification for the shortest path flow information from one symptom to another in these networks (Borgatti, 2005).

It is of course possible that different definitions of centrality may not end up affecting the end result in terms of identifying influential nodes. That is, under different centrality definitions, the same symptom might appear to be "most influential". If this were true, then the need for a clear justification for the selected definition of centrality would be ameliorated somewhat. To test this idea empirically, we used two publicly available samples and examined how changing the definition of betweeness centrality from the shortest path length (Freeman betweenness) to a one that uses random walk (random walk betweenness) or a weighted combination of all walks (communicability betweenness) can alter this centrality index (Estrada, 2016; Freeman, 1978; M. E. J. Newman, 2005).

We also showed how the ranks of nodes change depending on the definition used, which again highlights the point that different definitions of centrality candidate different

nodes as being more influential and if we want to interpret them in the clinical context we need to first decide which definition is appropriate for the psychopathology networks to pick. To illustrate the significance of this point more clearly, we offer the following example. In Figure 1.C. (average cross-sectional network), even though the shortest path between irritability and anger is the direct edge between them, it might very well be the case that when someone becomes angry, they feel guilty because of the anger and this guilt makes them worried about their performance. As a result they become irritable. In other words, activation of anger does not automatically imply activation of irritability (which is the conclusion if we believe that information flows through the shortest path), but the information might follow a random path (Ang->Glt->Wrr->Irr) to activate irritability. Given our results suggesting that different centrality definitions yield identify different symptoms as being particularly important, a better understanding of the precise mechanisms through which symptoms interact is needed.

In study 2, we tested a second common assumption when interpreting networks models derived from cross-sectional datasets. A careful reading of the psychopathology network literature reveals that even though the cross-sectional networks are undirected and contain no temporal information, researches draw inferences and make conclusions about the dynamics of the symptom-symptom interactions.

To test the validity of these conclusions, we created cross-sectional networks for each time point of three time-series datasets. If it is justified to use cross-sectional network to reveal the dynamics of the symptoms and their interactions, then cross-sectional networks of a time-series dataset should be similar to the temporal network of the dataset. Based on metrics used in previous network papers (Bos et al., 2017; Fried et

al., 2018), we defined our similarity metrics as: Edges Present (the number of times that if an edge is present in the temporal network, it is also present in the cross-sectional network), Edges not Present (the number of times that if an edge is not present in the temporal network, it is also not present in the cross-sectional network), Sign change (the percent of edges that change sign in cross-sectional networks), Correlations (correlation between edge weights of the cross-sectional networks and the temporal network), Top6 Edges (percent of the cross-sectional networks that have the same top 6 edges of the temporal network), centrality measures (betweenness and closeness centrality).

The average proportion of Edges Present was 79.4 across the four samples, suggesting fairly strong overall agreement between cross-sectional and temporal estimates of edges present. This was in contrast with the proportion of Edges not present, which was 42.15 averaged across the four samples. This means that cross-sectional networks are better at picking up edges that are present in the temporal network and not necessarily identifying the symptoms that do not interact with each other in the temporal network. Consequently, cross-sectional networks may overestimate edges in temporal networks, which could reduce the validity of inferring temporal network properties.

Additionally, the 59.67% Sign Change averaged over all the four samples shows that if a researcher chooses time A as her window of time to fit cross-sectional network, she might not only get a different edge weights, as depicted by the low value of Top 6 Edges (16.48%), but also a different sign for the edges. This raises significant concerns regarding any conclusions made about the inhibitory versus excitatory nature of interactions between symptoms when using a cross-sectional network. Finally, the correlations between cross-sectional networks and the temporal network edges ranged

between 0.42 and 0.73 among all samples. While this shows modest agreement, it does not support the conclusion that the cross-sectional networks reveal the same symptom-symptom interactions as the temporal network.

Importantly, the results described above were a comparison of cross-sectional and temporal network properties from the *same set of participants*. In essence, this is a fixed-effects comparison. In practice, results from cross-sectional network studies are not only generalized to temporal networks of the study sample, but presumed to generalize to the temporal dynamics of other samples. To test this assumption of generalizability, we divided our largest data set in half, and fit a cross-sectional network to the first half of participants and a temporal network was fitted for the second half. As can be seen in Table 1, this assessment of out-of-sample generalizability (i.e., random effects) resulted in significantly lower values almost all of our similarity metric components. Taken together, we believe these results suggest that greater restraint is necessary when interpreting cross-sectional network properties.

Limitations

While we believe the analyses presented above have significant merit, there are several key limitations. First, our analyses present a mainly descriptive account of differences between centrality definitions and cross-sectional vs. temporal networks. Reliance on the descriptive metrics is the major limitation of this paper and further analytical and simulation studies should be used to show the points raised in this empirical study in a more systematic and rigorous way. A second limitation worth mentioning is the relatively small size of sample 2.2, which was used for our "out-of-

sample" analysis. This was our largest sample (N=120) which we used to divide to two same size samples, and test the generalizability of cross-sectional networks. Nevertheless, this test and more generally study 2 can benefit from larger sample sizes and would give us a more accurate picture.

In this paper, we empirically studied the implicit assumptions made when interpreting the results derived from the psychopathology networks. Based on the similarity metric that we defined it can be seen that the cross-sectional networks cannot be used as the basis for interpretation of symptom-symptom interactions and how the symptoms (nodes) of the network influence each other.

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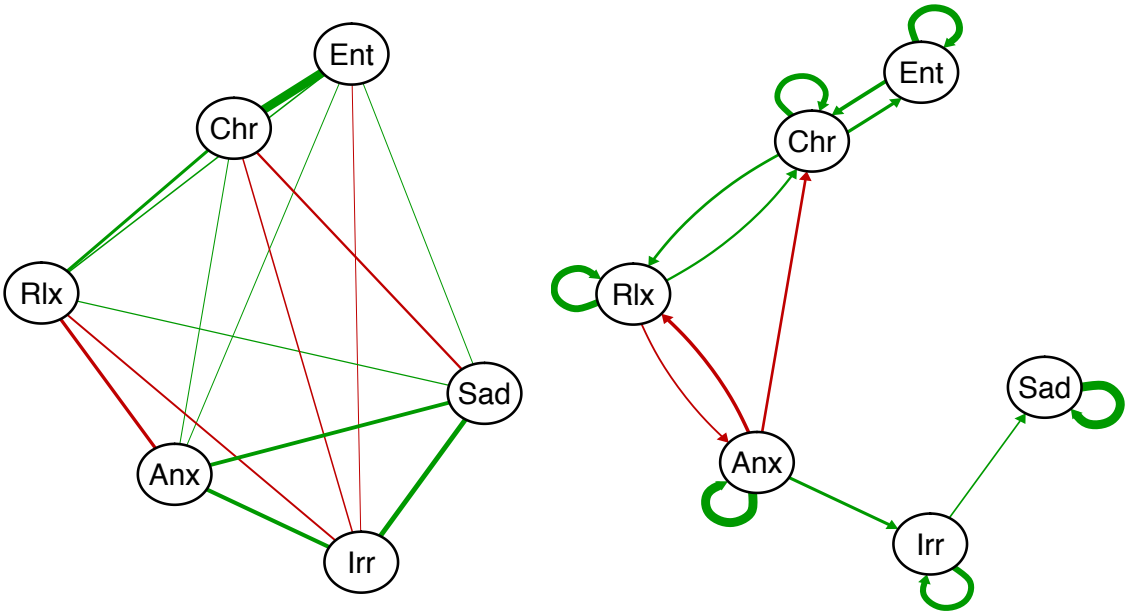
TABLES

Table 1. Summary of Results

Dataset	Edges Present	Edges not Present	%Sign Change	Correlations	Top 6 Edges
Bringmann (in sample)	84.82 (15.95)	41.97 (27.27)	27.78	0.73 (0.05)	11.67%
Fisher	61.70 (15.08)	64.85 (16.3)	57.14	0.63 (0.12)	30.68%
Treadway	90.18 (12.79)	30.58 (15.33)	87	0.63 (0.12)	8.57%
Bringmann (out of sample)	80.95 (12.90)	31.21 (18.93)	66.7	0.42 (0.1)	15%

FIGURES

FIGURE 1



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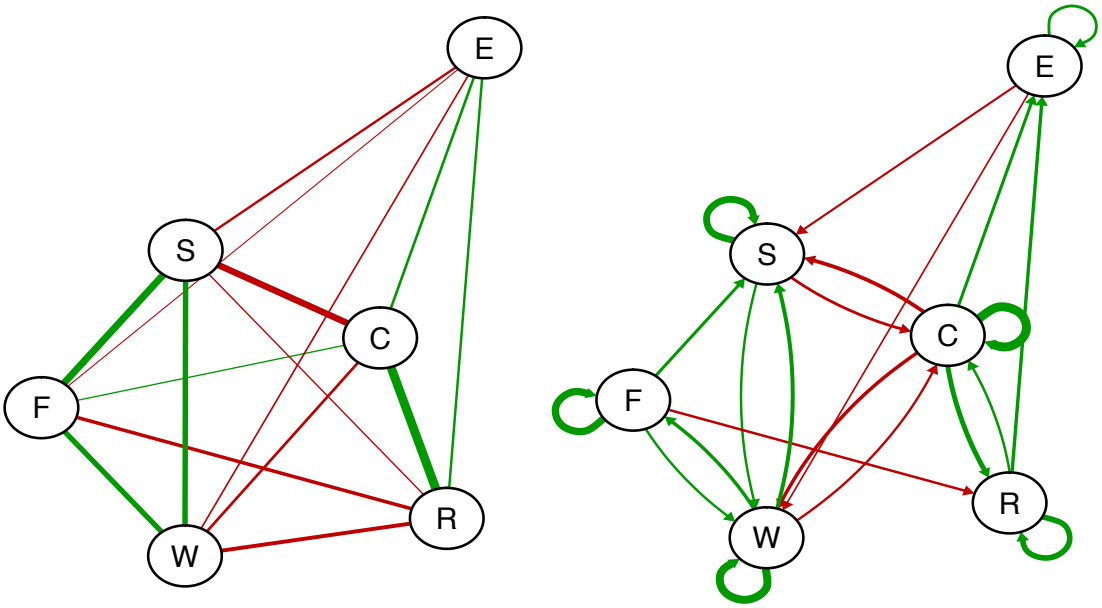

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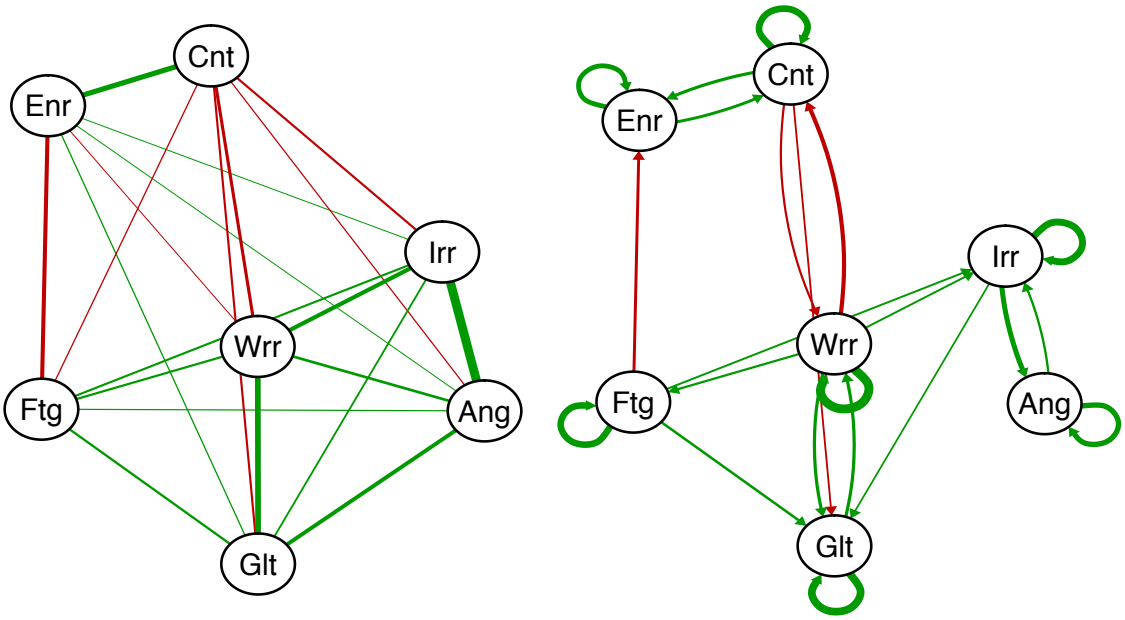
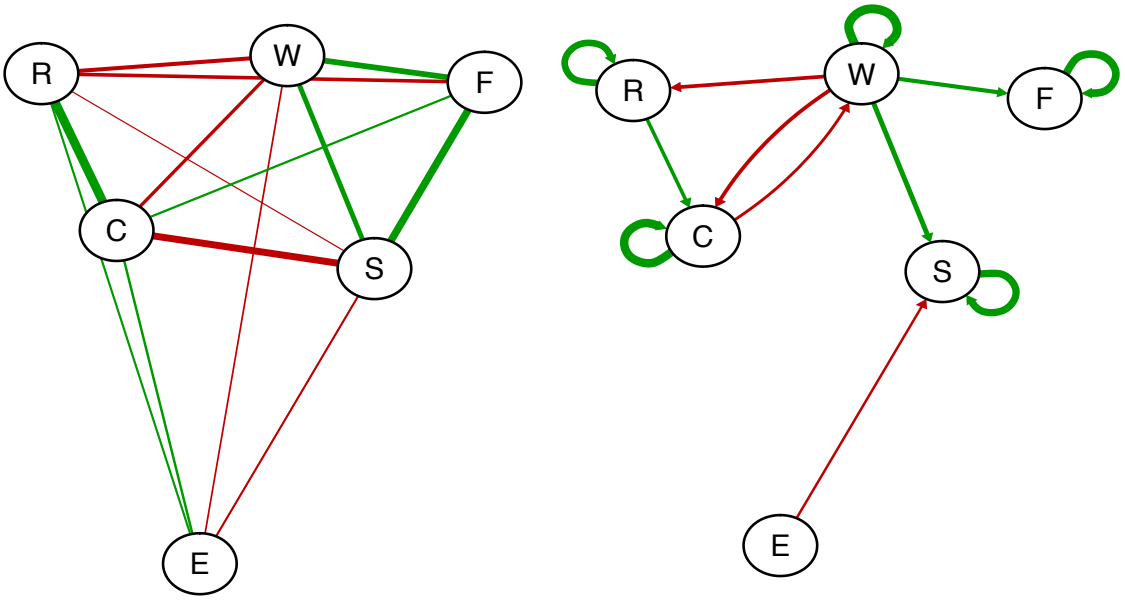


C.



D.

Figure 1.

(A) Sample 2.1 average cross-sectional and temporal networks. **(B)** Sample 2.2 (in sample) average cross-sectional and temporal networks. **(C)** Sample 2.3 average cross-

sectional and temporal networks. **(D)** Sample 2.2 (out of sample) average cross-sectional and temporal networks.

FIGURE 2

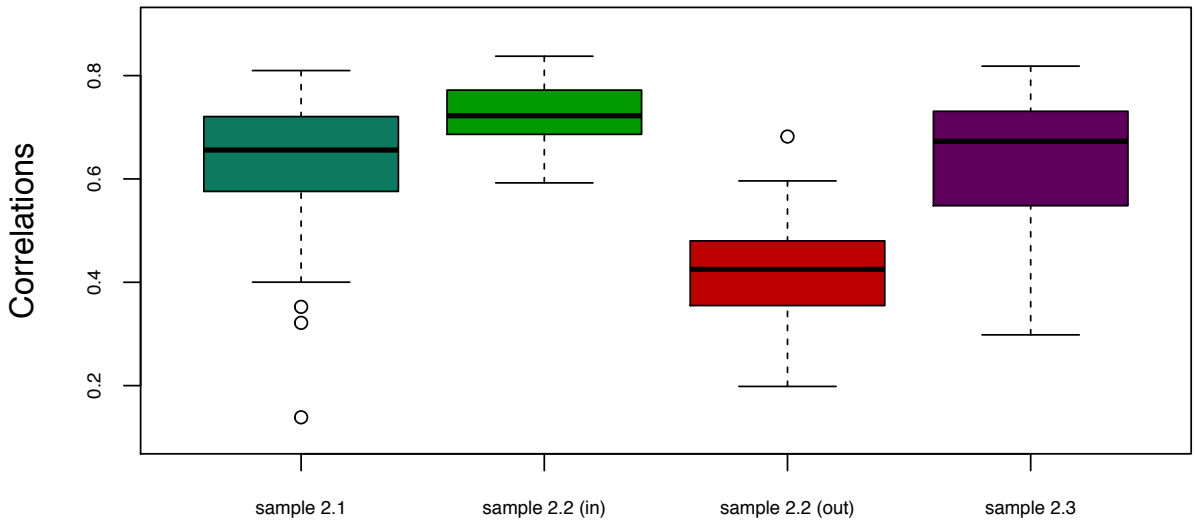
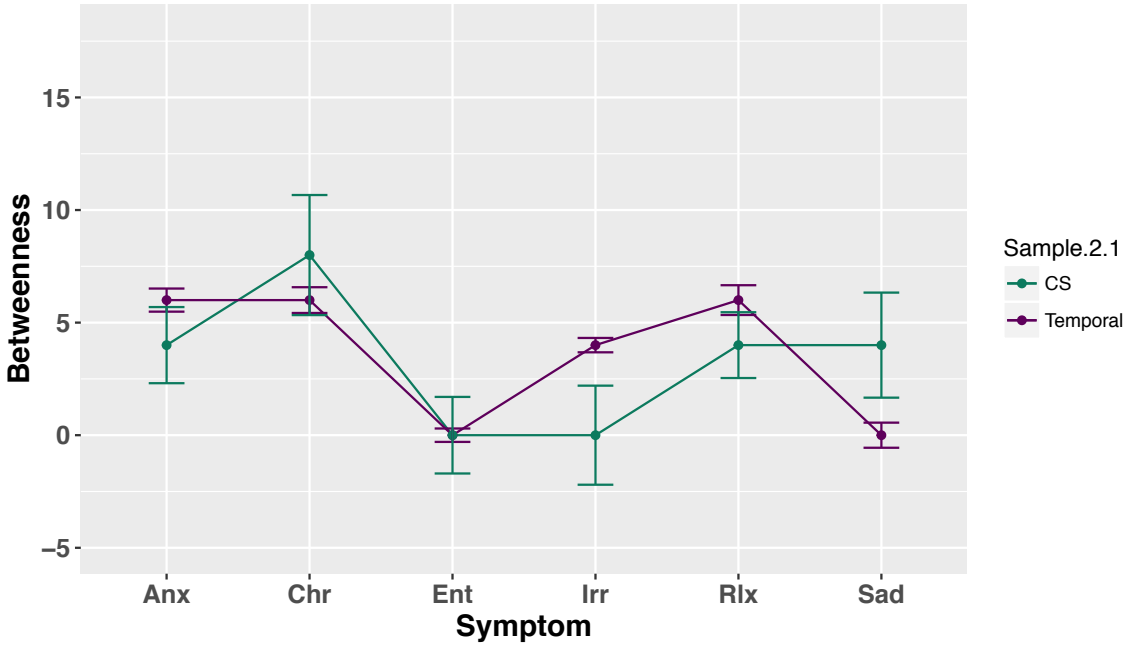


Figure 2.

Edge-Edge correlations between cross-sectional networks and the temporal network in each of the samples of study 2.

FIGURE 3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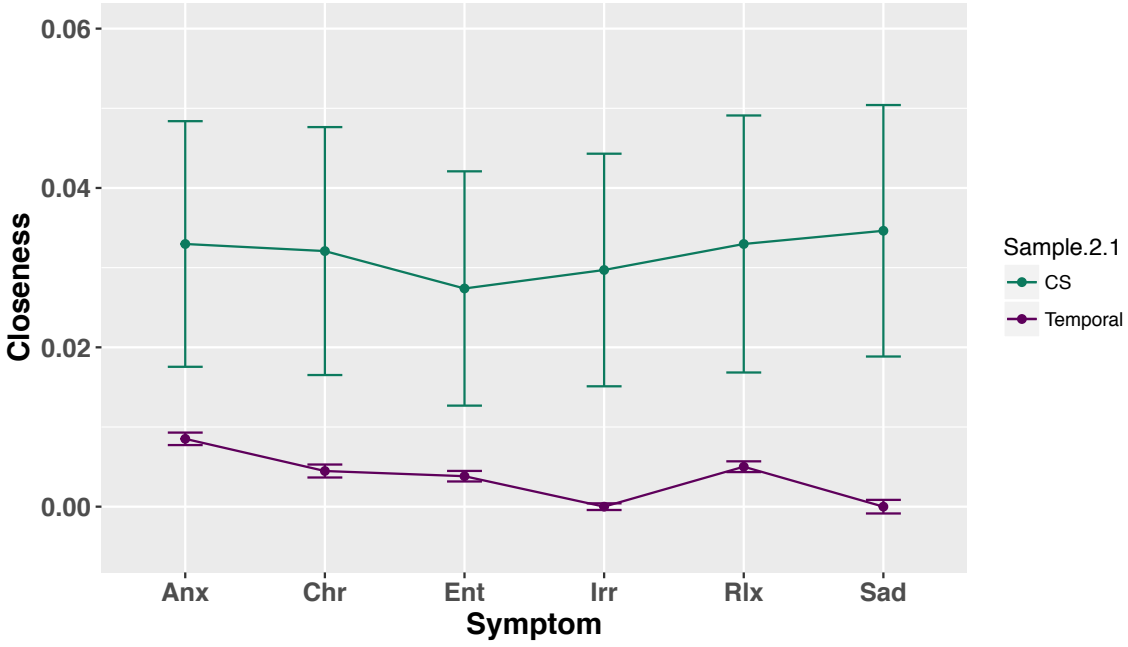
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Sample.2.1
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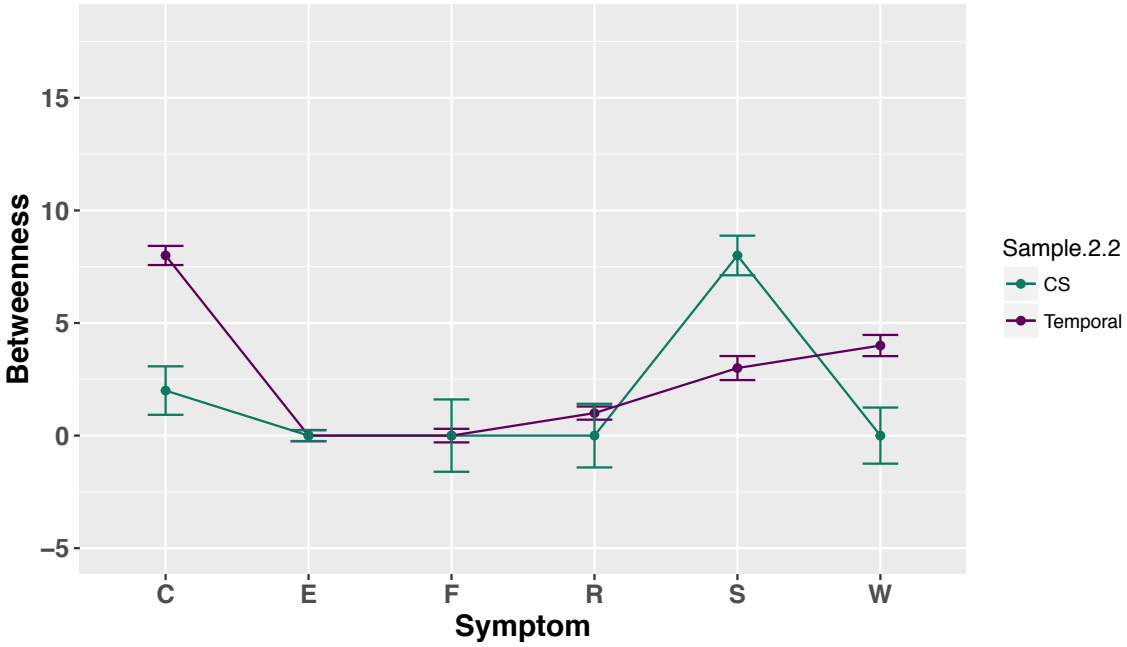
Temporal

B.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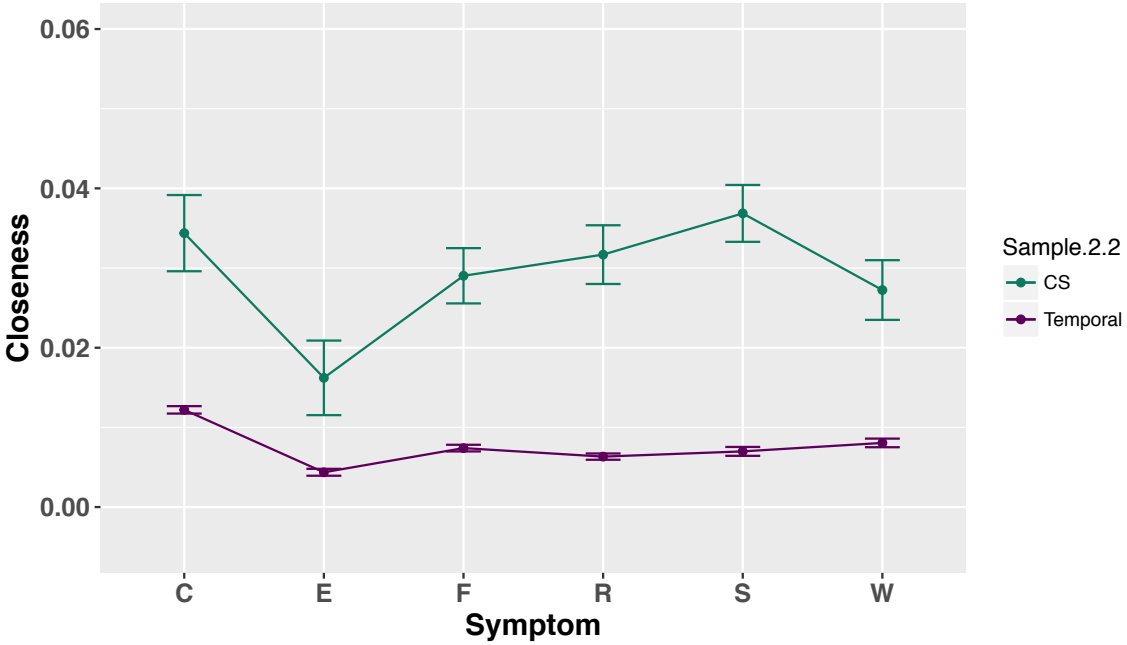
C.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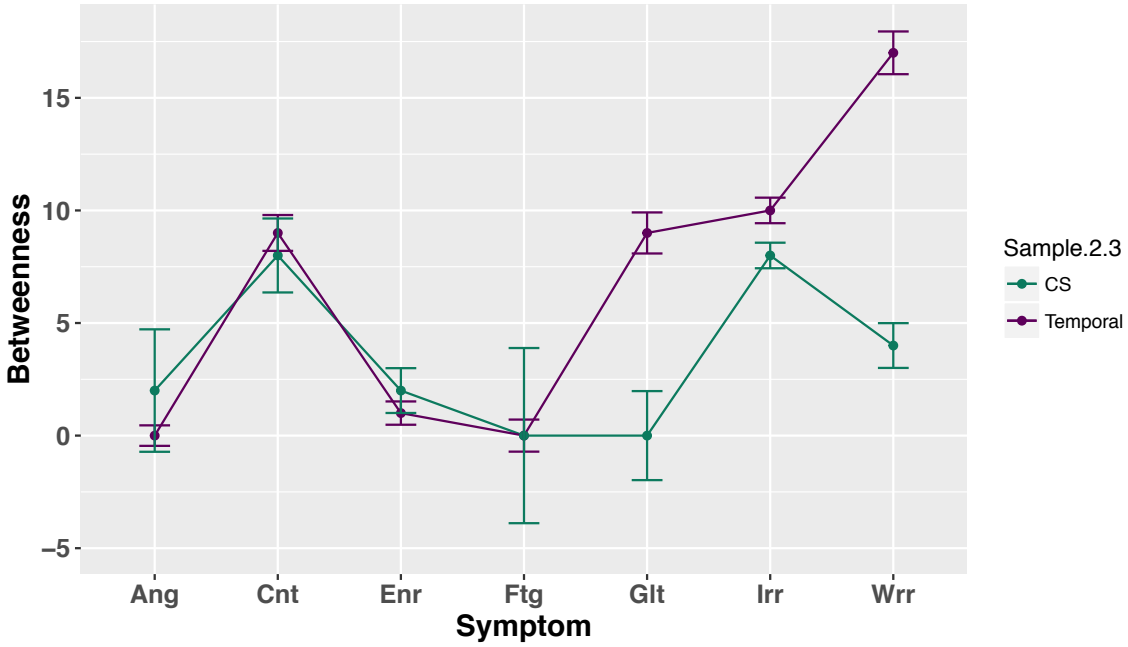
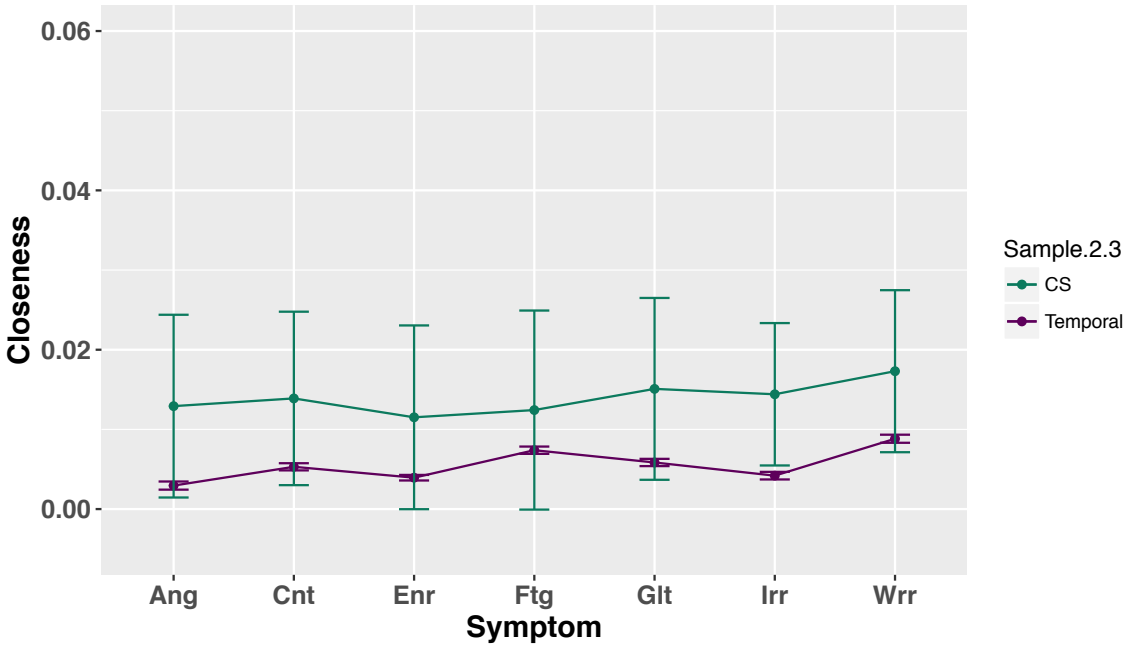
D.



E.



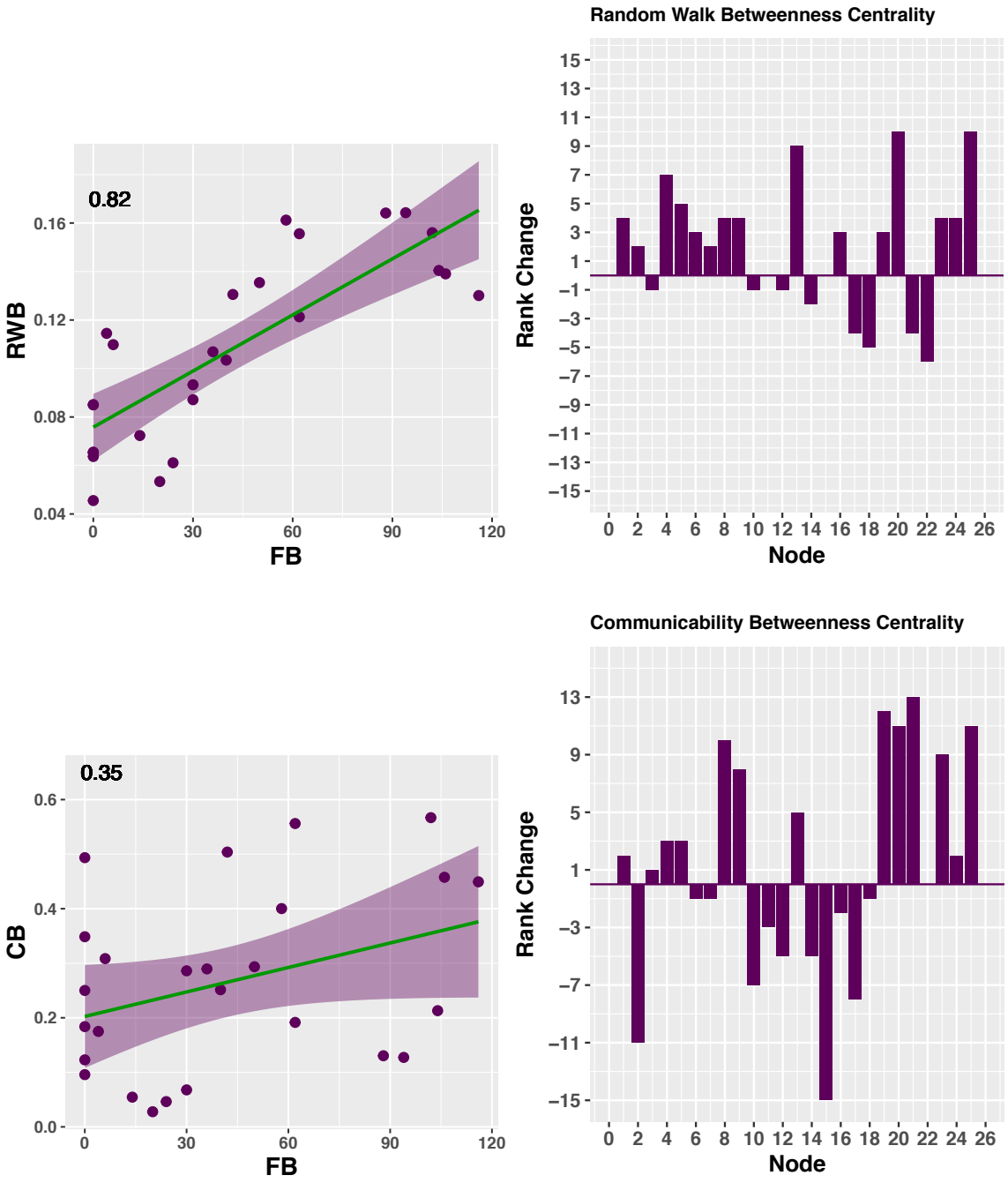
F.

Figure 3.

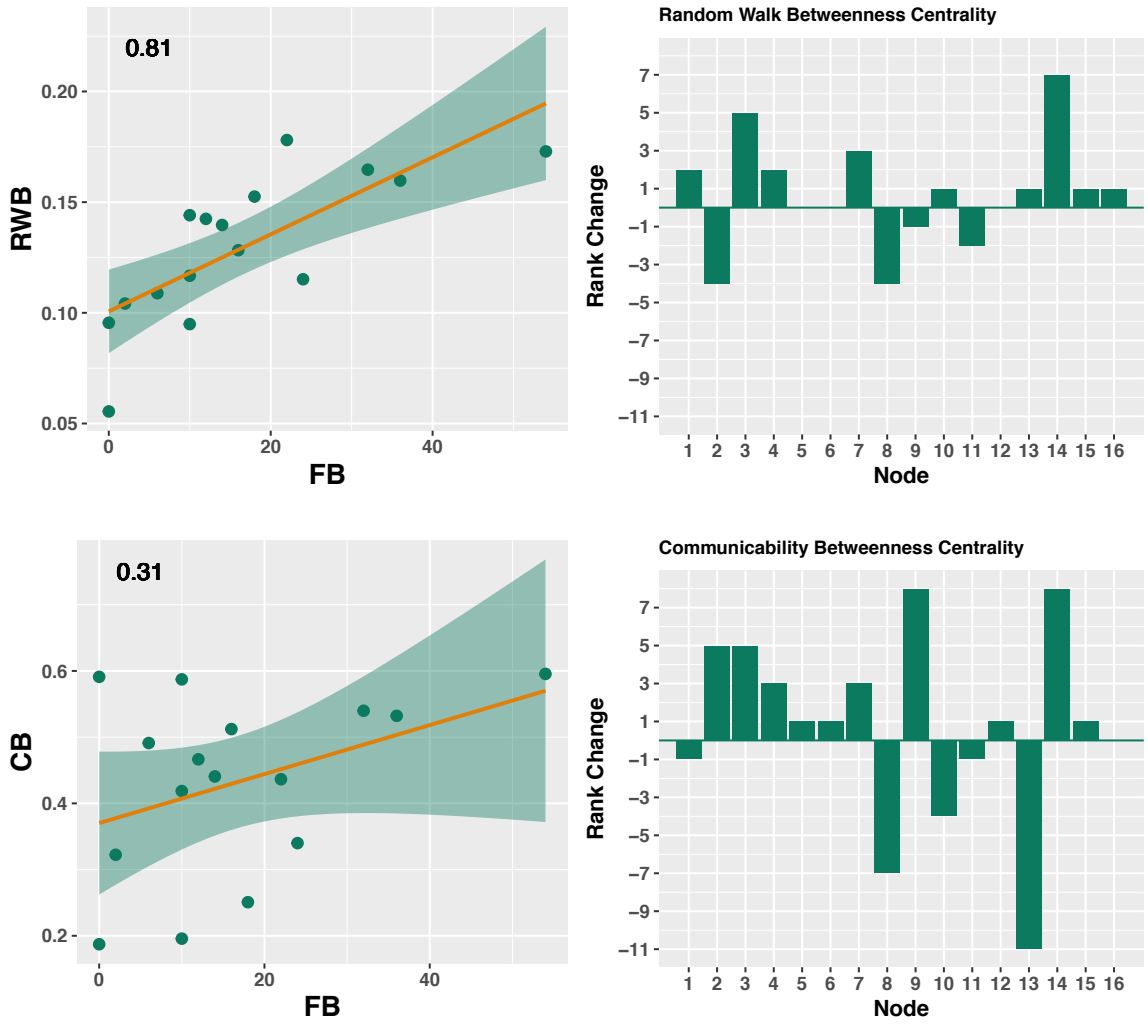
(A)-(B) Betweenness and closeness centrality for sample 2.1 temporal and average cross-sectional networks. The error bars for the temporal networks are derived by bootstrapping

each dataset 500 times and calculating the 95% CI of the centrality values. The error bars for the average cross-sectional network are the median of half the range of centrality values in each of the cross-sectional networks of each sample. **(C)-(D)** Betweenness and closeness centrality for sample 2.2 temporal and average cross-sectional networks. **(E)-(F)** Betweenness and closeness centrality for sample 2.3 temporal and average cross-sectional networks.

FIGURE 4


0.82
RWB
FB
Random Walk Betweenness Centrality
Rank Change
Node
0.35
CB
FB
Communicability Betweenness Centrality
Rank Change
Node

A.



B.

Figure 4.

(A) Comparison of RWB and CB definitions with those of Freeman (FB) for sample 1.1. The spearman correlation between RWB and FB, and CB and FB are also written on the graphs. **(B)** Comparison of RWB and CB definitions with those of Freeman (FB) for sample 1.2. The spearman correlation between RWB and FB, and CB and FB are also written on the graphs.