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Research paper

Taxonicity and network structure of generalized anxiety disorder and major depressive disorder: An admixture analysis and complex network analysis

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ABSTRACT

Background: Recent years have witnessed sustained efforts to delineate the nosology of generalized anxiety disorder (GAD), especially in light of its substantial comorbidity with major depressive disorder (MDD). Traditional diagnostic conceptualizations regard these disorders as categorically distinct; however, extant literature attests to appreciable similarities. The application of admixture analyses and complex network analyses has become more prevalent in recent years to investigate the presence of meaningful subgroups in mental disorders and to address qualitative similarity in network structure across disorders. To date, no studies have extended these analytic techniques to determine whether GAD and MDD constitute independent syndromes. The current study used a clinical sample comprising individuals diagnosed with primary GAD or primary MDD to examine potential subgroups and network structure using symptoms of each disorder as indicators.
Methods: The current sample comprised 111 individuals who received primary diagnoses of either GAD or MDD and completed a battery of assessments related to anxiety and depression.
Results: Results of the admixture analyses converged on a single class solution, suggesting that individuals with GAD derive from the same population as those with MDD. Furthermore, results of the complex network analyses did not reveal differences in centrality parameters across disorders, suggesting qualitative similarity.
Limitations: The cross-sectional nature of this study precludes conclusions about the temporal and causal dynamics of these disorders
Conclusion: GAD and MDD exhibit robust similarities, as evidenced by the converging results of the admixture analyses and complex network analyses. This conclusion complements the findings of transdiagnostic research, which has identified common mechanisms underlying multiple emotional disorders.

In recent years, extensive debate and controversy have ensued over the nosological status of anxiety and depressive disorders. In light of their high comorbidity (Kessler et al., 2005), comparable response to therapeutic interventions (Butler et al., 2006; Hofmann et al., 2012), and etiological similarities (Ask et al., 2015), anxiety and depressive disorders have become the object of sustained attention with novel classification paradigms being postulated to elucidate the core components underlying these forms of psychopathology (e.g., Research Domain Criteria, RDoC) (Insel, 2014). These issues have been especially acute for generalized anxiety disorder (GAD). An extensive literature has emerged underscoring the substantial overlap between generalized anxiety disorder and major depressive disorder (MDD). Approximately 60–70% of individuals diagnosed with GAD have received a lifetime diagnosis of MDD (Carter et al., 2001), and this comorbid presentation occurs as often, if not more often, than pure presentations of GAD and MDD (Mineka et al., 1998). Etiological research has substantiated considerable genetic similarities between these syndromes (Hettema et al., 2006), indicating the presence of common temperamental vulnerabilities and distal risk factors (Brown and Barlow, 2009).

Although several studies have explicated *quantitative* differences between these disorders (Mennin et al., 2008; Miranda and Mennin, 2007), further research is warranted to address the presence of *qualitative* differences. Differential relationships between

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various symptoms and each disorder may be still consistent with a model that construes GAD and MDD as qualitatively similar (i.e., quantitative differences may be present even if individuals with primary GAD derive from the same population as those with primary MDD). Indeed, efforts to delimit the boundaries of GAD have often eventuated in doubt about the specificity of its symptoms (Ruscio, 2002). Goldberg (1996) ascertained that depression and anxiety are poorly represented by a taxonic nosology, in light of the substantial similarities between these two constructs. Increasing disappointment in the utility of conceptualizing these disorders as taxonic and mutually exclusive has inaugurated proposals for dimensional frameworks (Brown and Barlow, 2009) and complex network approaches (Borsboom and Cramer, 2013; Hofmann et al., in press).

The dimensional approach posits a hierarchical conceptualization of anxiety and depressive disorders such that higher-order constructs (e.g., neuroticism/behavioral inhibition and positive affectivity/behavioral activation) account for overlap across more specific manifestations of psychopathology (Brown and Barlow, 2009). As a wealth of literature attests to the presence of common etiological factors and transdiagnostic mechanisms (Barlow et al., 2014), evidence of qualitative similarity between GAD and MDD would confirm a dimensional model, which could have important treatment implications. Namely, evaluating which nosology best reflects the covariation between GAD and MDD could determine the appropriateness of using transdiagnostic interventions as opposed to disorder-specific treatments.

Complex network approaches do not require that symptoms be the direct consequence of a latent disease construct (e.g., MDD or GAD). Instead, symptom covariation arises in virtue of a complex network structure whereby mutually reinforcing causal relations abide among symptoms (Borsboom and Cramer, 2013; McNally et al., 2014; Robinaugh et al., 2014). The relative importance of a given symptom may be evaluated by considering centrality parameters, which index the overall connectivity of a symptom (Borsboom and Cramer, 2013). Investigation of the complex network structure of GAD and MDD can elucidate the presence of qualitative differences between these disorders.

In the current study, we performed admixture analyses on a sample of individuals diagnosed with either GAD or MDD to determine the number of populations of origin. This analytic approach possesses several advantages over other commonly used techniques (e.g., cluster analyses, factor analyses, etc.). Whereas cluster analyses constitute a type of non-inferential technique often used for data reduction purposes, admixture analyses permit statistical inference. Factor analytic techniques invoke continuous latent variables to explain associations between observed variables, which does not provide information regarding the number of classes or subgroups. Admixture analyses, however, estimate the number of qualitatively distinct populations of origin underlying a sample. Although several studies have employed this analytic approach to examine the presence of subgroups in mental disorders (e.g., social anxiety disorder, bipolar disorder, agoraphobia, etc.) (Aderka et al., 2012; Ortiz et al., 2011; Tibi et al., 2015), none to date have conducted admixture analyses to address issues related to the nosology of GAD and MDD. Results of a complex network analysis may complement those of an admixture analysis. If admixture analyses substantiate a single population of origin as the best fitting model, then examination of complex network structures may further inform whether these disorders differ qualitatively.

Methods.

Participants.

The current sample comprised 111 individuals who were seeking treatment at an anxiety and mood disorders clinic in the Northeastern United States. Participants were assessed by doctoral student clinicians using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders and received diagnoses of anxiety disorders (e.g., generalized anxiety disorder, social phobia, panic disorder, specific phobias, etc.) and mood disorders (e.g. depression, dysthymia, etc.) (First and Spitzer, 2002). Diagnoses were reviewed by supervising clinicians and determined by consensus using the clinical severity ratings (CSR). Inter-rater reliability between supervisors and doctoral clinicians (ICC=0.77) was considered excellent according to the cut-off criteria proposed by Cicchetti (1994) (≤ .75–1.00). Overall, 70 (63.01%) individuals received a primary diagnosis of GAD, and 41 (36.99%) individuals received a primary diagnosis of MDD. Moreover, those in the former group lacked a comorbid diagnosis of MDD, and those in the latter group lacked a comorbid diagnosis of GAD. It should be noted that hierarchical exclusion criteria for GAD and MDD were not applied. Exclusion criteria included clinically significant signs of psychosis or any organic mental disorders. No participants in this sample met exclusion criteria. An institutional review board approved the study, and informed consent was obtained from participants before inclusion. Demographic information is presented in Table 1.

Table 1
Demographic and clinical measures.

	GAD ($n=70$)	MDD ($n=41$)	Statistic	p
Gender				
Male	19 (27%)	16 (39%)	$\chi^2(1)=1.69$	0.19
Female	51 (73%)	25 (61%)		
Ethnicity				
Caucasian	61 (87%)	31 (76%)	$\chi^2(1)=2.42$	0.12
Non-Caucasian	9 (13%)	10 (24%)		
Comorbidity			$\chi^2(1)=0.29$	0.59
With Comorbid	14 (20%)	10 (24%)		
Without Comorbid	56 (80%)	31 (76%)		
Age	35.17 (12.39)	33.27 (14.41)	$t(109)=-0.71$	0.48
BDI-II	18.69 (10.29)	22.52 (11.89)	$t(109)=1.71$	0.09
STAI-T	53.59 (9.97)	54.34 (9.40)	$t(109)=-0.39$	0.69
CSR	5.47 (1.30)	5.00 (1.43)	$t(109)=-1.72$	0.09

Note. BDI-II = Beck Depression Inventory-II; STAI-T=State Trait Anxiety Inventory, Trait Scale; CSR = Clinical Severity Rating.

Measures.

1. State trait anxiety inventory, trait scale

The State Trait Anxiety Inventory (Spielberger, 1983; Spielberger et al., 1970) consists of two 20-item scales that assess and differentiate between state and trait anxiety in adults: State and Trait. Trait anxiety (T-Anxiety) refers to relatively stable individual differences in anxiety proneness as a personality trait. The trait anxiety scale was used in the current study to examine stable characteristics of anxiety, thereby increasing comparability with our other primary measure, which assesses stable characteristics of depression. Participants respond using a four-point Likert scale ranging from 1 (*almost never* or *not at all*) to 4 (*almost always* or *very much so).* Scores vary from a minimum of 20 to a maximum of 80. The STAI Trait scale has been found to have excellent internal consistency ($\alpha=.86$ to.92) and levels of test–retest stability that would be expected for a trait measure (e.g., test–retest correlations across 1–4 months range from.73 to.86), (Spielberger et al., 1983).

2. Beck Depression Inventory II

The BDI-II (Beck et al., 1996) is a 21-item instrument designed to measure both the presence and severity of depressive

symptoms. Each item consists of a group of four statements that range in intensity (e.g. from "I do not feel sad" to "I am so sad or unhappy that I can not stand it"). The BDI-II is scored by assigning a value from 0 to 3 to each answer and summing these values to derive a total score (0–63). The BDI-II has been shown to have excellent internal consistency (α=.90) and good psychometric properties (Wang and Gorenstein, 2013).

3. Clinical severity rating

Diagnosticians assigned clinical severity ratings (CSRs) to index the overall severity of each disorder with which an individual presents. The scale ranges from 0 to 8, with higher levels of severity reflected by higher scores. This psychometrically valid measure was adapted from the CSR scales utilized by Brown et al. (2001).

Data Analytic Strategy.

Admixture Analyses.

To determine number of normally distributed populations of origin for the current sample, we utilized admixture analyses. This analytic framework employs maximum likelihood estimation to compute the probability that the observed data would occur assuming *k* Gaussian distributions. We conducted admixture analyses on the current sample to obtain fit values for up to four populations of origin, which would better enable us to ascertain the most likely number of populations of origin.

Interpretation of results are facilitated by way of likelihood ratio tests (LRTs) and the criteria proposed by Kolenikov (2001). Using LRTs, if the difference between log likelihood values is significant according to a χ^2 distribution with 3 degrees of freedom and the log likelihood is greater for two populations of origin, then the hypothesis that the current sample emanates from only one population of origin can be rejected (Aderka et al., 2012; Bellivier et al., 2001; Delorme et al., 2005). Moreover, Kolenikov (2001) recommended that the model associated with the largest χ^2 goodness-of-fit p-value indicates the most likely number of populations of origin.

To foster greater confidence in the soundness of our results, we conducted these analyses using measures of both anxiety and depression, as converging evidence about model fit from each symptom cluster may be a more robust indicator of the extent of overlap between these two disorders. All admixture analyses were conducted with STATA 13 using the denormix script developed by Kolenikov (2001). Differences in demographic and clinical measures were also examined across both diagnostic groups.

Complex Network Analyses.

To interrogate the complex network structure of GAD and MDD, symptoms of anxiety and depression were modelled using the R package *qgraph* (Epskamp et al., 2012). Each item on the STAI-T and the BDI-II was modelled as a symptom *node* of anxiety and depression, respectively. Reverse scored items were included when appropriate. *Edges* between symptom nodes reflected partial correlation coefficients as estimated by the *glasso* procedure. That is, each edge reflects a unique association between two symptom nodes controlling for all other relationships in the network. Furthermore, a cut-off threshold of 0.30 was imposed to omit weak associations.

The principal centrality parameter emphasized in the current study is node strength, which denotes the sum of all associations between a particular node and all other nodes. Additionally, node strength is robustly associated with other centrality parameters (e.g., betweeness, closeness, etc.) and, thus, serves as a good metric to quantify network stability (Fried et al., 2016). Two-sided permutation tests were conducted to determine whether individuals with GAD and MDD significantly differ on mean node strength, which would suggest qualitative differences in connectivity across disorders. Furthermore, permutation tests were conducted to determine whether node strength differed between anxiety and depression symptoms within both the GAD network and the MDD network, which would illuminate whether a certain symptom cluster (i.e., depression symptoms or anxiety symptoms) is more important in a certain disorder network (i.e., MDD or GAD).

Results.

4. Demographic and clinical differences

Individuals were compared on demographic and clinical characteristics across diagnostic category (Table 1). As no statistically significant differences emerged, the current results suggest a potential lack of dissimilarity between GAD and MDD with respect to demographic and clinical profiles.

5. Admixture analyses

We conducted admixture analyses with measures of both anxiety and depression (i.e., STAI-T and BDI-II), by computing the estimated log likelihood and chi-square goodness of fit for models with one, two, three, and four normally distributed populations of origin (Table 2). With respect to anxiety, results from the likelihood ratio test indicated that a model with two populations of origin did not significantly diminish the deviance ($\chi^2_{Diff}=1.30$, $p=$n.s.), suggesting that the model with a single population yields the best fit and greater parsimony. Examination of the chi-square goodness of fit index corroborated the results of the likelihood ratio tests, as the model with one population was associated with the highest probability value ($\chi^2_{(4)}=1.24$, $p=0.87$). This single population possessed a mean of 54.06 (95% Confidence Interval=52.29-55.84) and a standard deviation of 9.53 (95% Confidence Interval=8.96-10.11). Please refer to Fig. 1 to inspect the kernel probability distribution of anxiety symptoms.

Reconducting these analyses with symptoms of depression as the outcome variable replicated the above pattern of results. The likelihood ratio test suggested that the model with two populations of origin did not significantly improve model fit, supporting the single population model ($\chi^2_{Diff}=4.57$, $p=$n.s.). Furthermore, the chi-square goodness of fit index revealed that the single population model was associated with the highest probability value

Table 2
Admixture analyses.

	Anxiety Symptoms (STAI-T)			Depression Symptoms (BDI-II)		
	Log Likelihood	$\chi^2(df)$	*p*	Log Likelihood	$\chi^2(df)$	*p*
Single population	−407.83	1.24 (4)	0.87	−419.35	2.95 (4)	0.57
Two populations	−406.53	12.46 (2)	0.002	−414.88	3.61 (2)	0.16
Three populations	−403.57	5.15 (2)	0.07	−411.14	2.38 (2)	0.30
Four populations	−400.32	2.68 (2)	0.26	−413.67	2.88 (2)	0.24

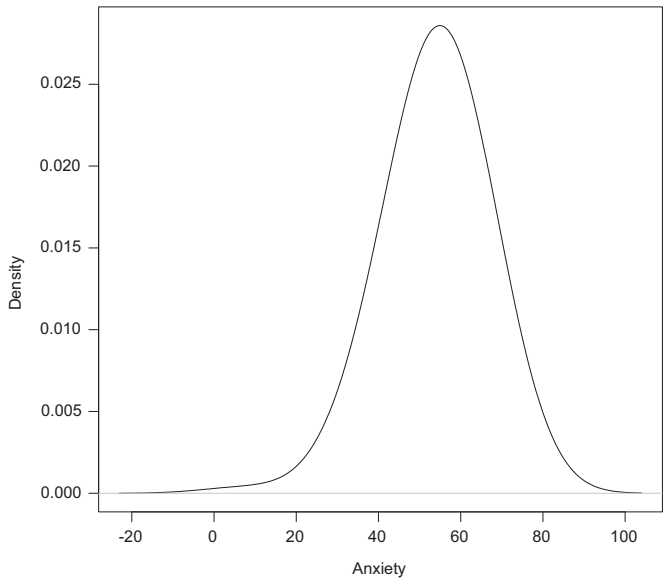

Fig. 1. Kernel probability distribution for anxiety.

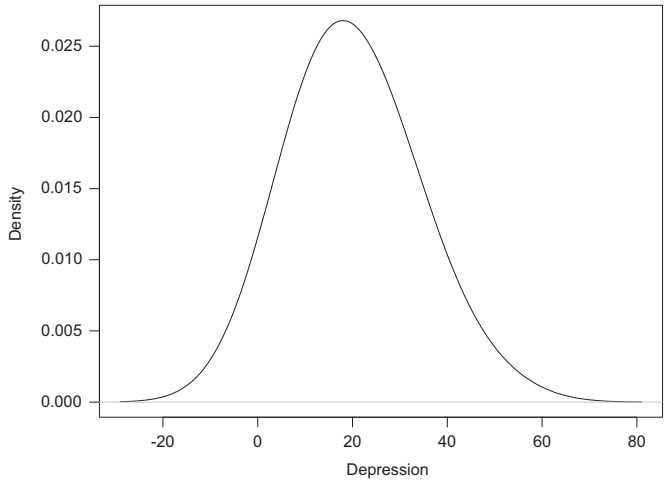

Fig. 2. Kernel probability distribution for depression.

($\chi^2_{(4)}=2.95$, $p=0.57$). For the BDI-II, this single population had a mean of 20.08 (95% Confidence Interval =18.04–22.13) and a standard deviation of 10.95 (95% Confidence Interval =10.33–11.57). Please refer to Fig. 2 to inspect the kernel probability distribution of depression symptoms. Thus, the results of both admixture analyses converged, substantiating a single population of origin for individuals diagnosed with primary GAD and those with primary MDD.

6. Complex network analyses

Given the fact that a single population of origin represented the best fitting class solution, the complex network structure was estimated to further examine the presence of qualitative differences. The 20 anxiety symptoms and 21 depression symptoms were modelled as nodes in both the GAD individuals and MDD individuals. In both the GAD and MDD groups (Figs. 3 and 4, respectively), visual inspection of the complex network plots reveals that symptoms of anxiety and depression are central to each group. As indicated by the strength plots (Figs. 5 and 6), symptoms of both anxiety and depression exhibited high strength in the GAD and MDD groups. Thus, it appears that anxiety and depression symptoms contribute to the overall pathology exhibited by individuals in both disorder groups, indicating potential qualitative similarity.

To quantitatively examine the degree of similarity between GAD and MDD, several permutation tests were conducted. It was revealed that the overall node strength of individuals with GAD did not significantly differ from those with MDD ($z=-1.64$; $p=0.10$). Next, the relative contribution of anxiety and depression symptoms were examined within each disorder network. Among individuals diagnosed with GAD, the node strength of anxiety symptoms did not significantly differ from the node strength of depression symptoms ($z=-1.25$; $p=0.21$). Among those diagnosed with MDD, the strength of depression symptoms did not significantly differ from the strength of anxiety symptoms ($z=-0.51$; $p=0.61$). Thus, the current pattern of results substantiates high levels of qualitative similarity between GAD and MDD, which is consistent with the results of the admixture analyses.

7. Discussion

The lack of clear demarcation between GAD and MDD has long undermined the utility of categorical nosologies such as the DSM-5. Although prior research has identified some differences in the presentation of these disorders (Curtiss and Klemanski, 2014), such results might reflect quantitative rather than qualitative heterogeneity. Results of the current study suggest that a high degree of qualitative similarity exists across both disorders, as the admixture model positing a single population of origin evidenced the best fit. Furthermore, these analyses were conducted using both anxiety symptoms and depression symptoms as indicators, and converging evidence in support of the single population model was obtained. The results of the complex network analyses complemented those of the admixture analyses, suggesting that neither anxiety nor depression symptoms were more central to GAD or MDD. Furthermore, overall node strength did not differ between GAD and MDD. Pairwise comparisons of each disorder on clinical and demographic characteristics comported with these analyses, indicating no significant differences with respect to anxiety symptoms, depression symptoms, and disorder severity. The overall pattern of results provides consistent evidence of appreciable overlap between GAD and MDD.

A substantial literature underscores a need for nosological frameworks that better delineate the essential components underlying anxiety and depressive disorders (Borsboom and Cramer, 2013; Brown and Barlow, 2009). Shared psychological factors that contribute to the pathogenesis and maintenance of GAD and MDD include emotion dysregulation and avoidance, neuroticism, repetitive negative thinking, and excessive reactivity to unwanted emotions (Barlow et al., 2014; Curtiss and Klemanski, 2014; Mennin and Fresco, 2013, 2015). Furthermore, similar genetic and neurological correlates are implicated in the expression of these disorders (Etkin and Schatzberg, 2014). Alternative conceptualizations of GAD and MDD may mitigate current obstacles inherent in the diagnosis and treatment of these disorders.

At least two frameworks might furnish plausible alternatives to categorical interpretations of GAD and MDD. For instance, the dimensional approach postulated by Brown and Barlow (2009) specifies higher order constructs under which more specific phenotypes of psychopathology are subsumed. That is, GAD and MDD proceed from an interaction of common genetic vulnerabilities and unique environmental conditions and, thereby, constitute differential expressions of a shared emotional psychopathology. Underlying each disorder are transdiagnostic mechanisms (e.g., experiential avoidance, anxiety sensitivity, emotional suppression,

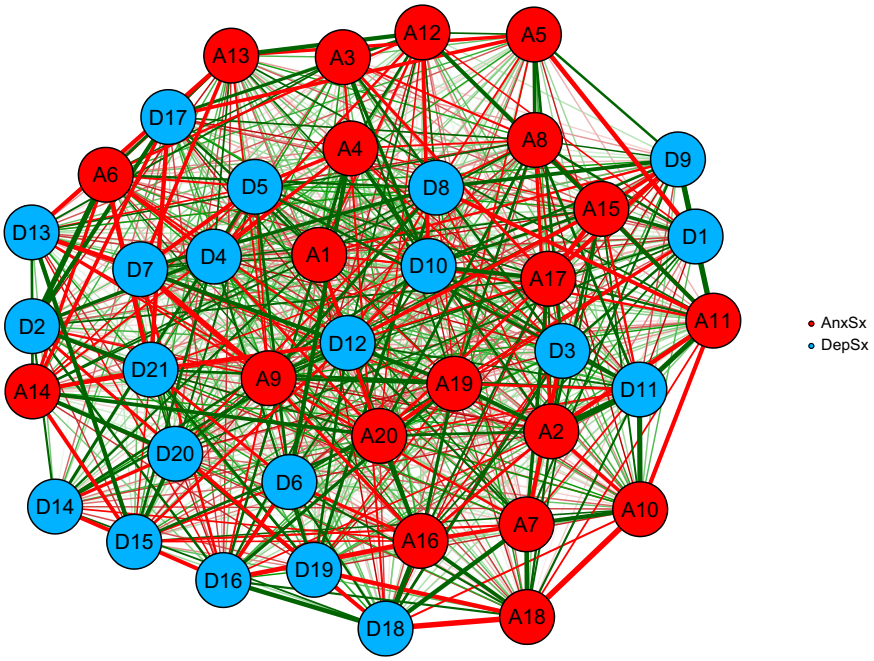

Fig. 3. GAD Complex Network.

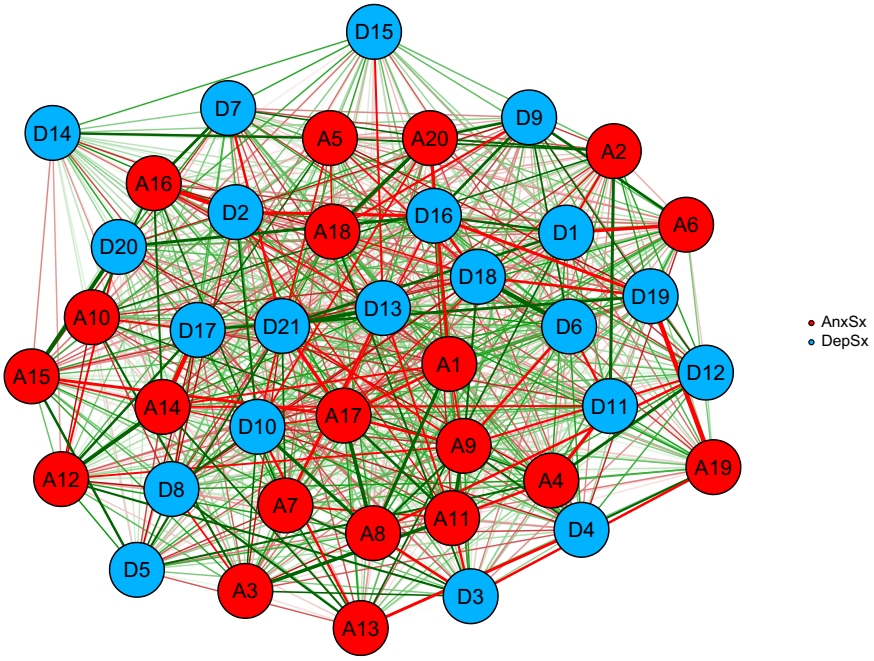

Fig. 4. MDD Complex Network.

and rumination) that maintain their pathological expression. According to this model, differences in the presentation of GAD and MDD would constitute trivial distinctions, especially considering the fact both disorders are amenable to substantial improvement with treatment protocols that target these transdiagnostic mechanisms (Norton and Barrera, 2012).

Another nosological model that has increasingly received attention is the complex causal network approach (Borsboom et al., 2011; Hofmann, 2014; Robinaugh et al., 2014). Rather than presuming that observed symptoms emanate from latent disease entities, the causal network approach posits that psychopathology emerges as a consequence of causally interrelated symptoms that stabilize into a state of disorder. Sophisticated statistical approaches have been recently applied to delineate the causal relationships among symptoms in emotional disorders (e.g., post-traumatic stress disorder) (McNally et al., 2014). Furthermore, the causal network model readily accommodates comorbidity, as networks are transdiagnostic in nature (Borsboom and Cramer, 2013; Borsboom et al., 2011). Accordingly, symptoms that manifest in both GAD and MDD can be the cause and consequence of "disorder-specific" symptoms. In accordance with the results of the current study, the substantial qualitative similarity across these disorders indicates that anxiety and depression symptoms are comparably central to each disorder, undermining the long-standing convention of conceptualizing GAD and MDD as categorically distinct entities.

By transcending the traditional diagnostic nomenclature that has persisted since the inception of the DSM-III, clinical

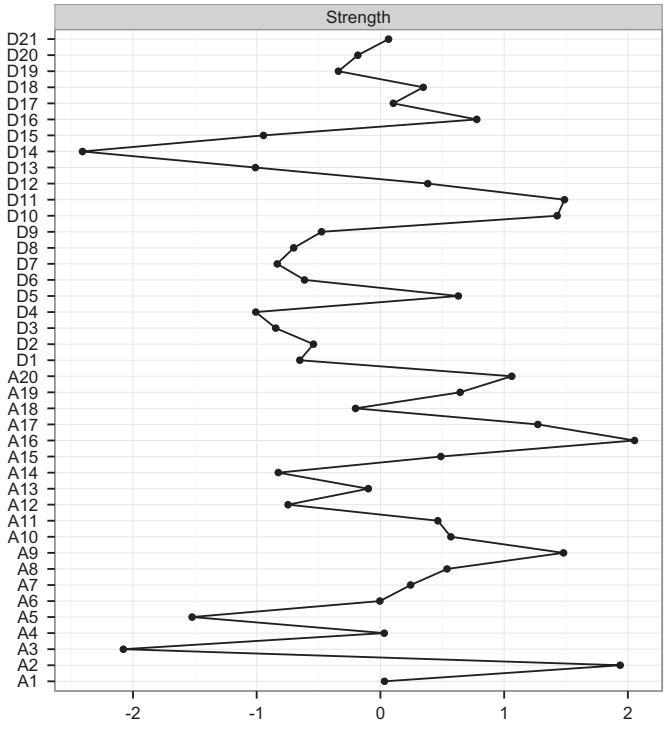

Fig. 5. Node strength of GAD group.

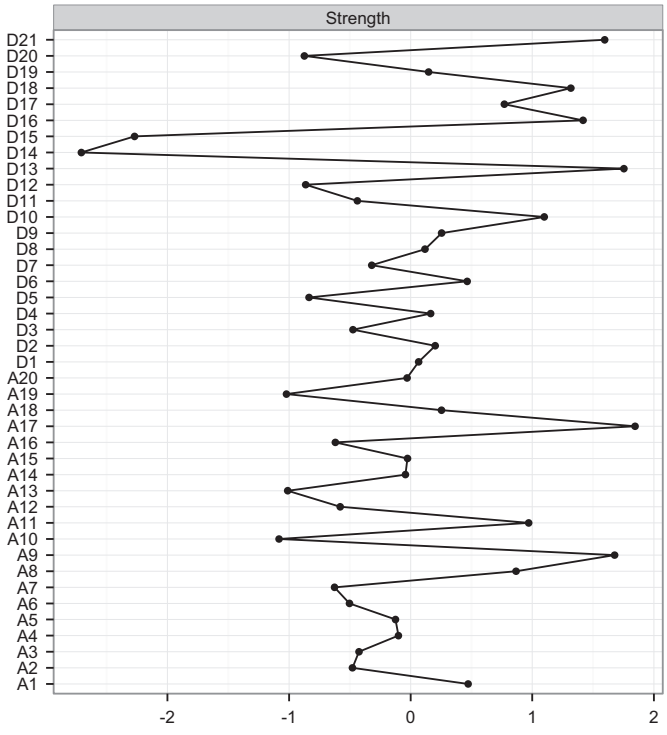

Fig. 6. Node strength of MDD group.

psychology might be able to achieve greater success in the treatment of individuals suffering from symptoms of GAD or MDD. Transdiagnostic interventions could qualify as an ideal treatment in this respect, as individuals with different primary diagnoses may undergo a single treatment that produces comparable therapeutic benefit (Barlow et al., 2014; Norton and Barrera, 2012). Consideration of underlying nosological issues can facilitate the development of maximally efficacious treatments.

Despite the convergence of results from both admixture analyses and complex network analyses, a number of limitations warrant mention. First, certain methodological considerations might undermine our conclusions (e.g., self-report, fixed order, etc.). Second, the cross-sectional nature of this study precludes causal interpretations. Third, a larger sample size would have been desirable to foster greater power for the admixture analyses to identify the appropriate class solution underlying this sample. The results of the current study would benefit from replication in larger sample sizes with greater power. It should be noted, however, that prior studies have conducted admixture analyses with comparable sample sizes ($n=161$) and have successfully identified relevant subgroups (Delorme et al., 2005). Furthermore, the application of such techniques as growth mixture modeling to longitudinal data would permit identification of subgroups in the developmental trajectories of GAD and MDD. That notwithstanding, the conclusions derived from the current study comport with extant literature, which emphasizes the appreciable symptomatic and phenotypic similarity persisting between GAD and MDD. The results of the admixture analyses were replicated using both anxiety symptoms and depression symptoms as indicators, thereby corroborating nosological models that do not assume mutual exclusivity between these disorders. Furthermore, the results of the complex network analyses substantiate symptomatic similarity between GAD and MDD. It would be profitable for future research to delineate more precisely the transdiagnostic mechanisms underlying these disorders.

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