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The Association of Life Stress With Substance Use Symptoms: A Network Analysis and Replication

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A growing body of evidence highlights the role of life stress as a risk factor for the development and relapse of substance use disorders (SUDs), but the relationship of life stress with the interactions among SUD symptoms is overlooked. The current study investigated the role of life stress in symptom networks of 3 different SUDs—alcohol, tobacco, and drug use—using the U.S. representative data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) I and II (N = 34,653). The symptom networks were estimated using the Ising model and l1-regularziation with model selection based on the Extended Bayesian Information Criterion. We examined the association of stress with 2 network characteristics: the network connectivity and the network structure. In addition, we applied bootstrap routines to examine the stability of our results and tested whether our findings of Wave 1 replicated in Wave II of the NESARC. For alcohol and drug use symptoms, but not for tobacco use symptoms, greater network connectivity (which is related to psychiatric severity and prognosis) was associated with the number of stressors. In contrast, the structure of SUD symptom networks remained stable regardless of the level of stress, which indicated that the order of central nodes in the symptom networks was not significantly associated with stress. Altogether, our findings suggest that there is a quantitative (i.e., greater connectivity), but not qualitative (i.e., structure), difference in alcohol and drug use symptom relationships associated with life stress.

General Scientific Summary

This study demonstrates that life stress is associated with denser relationships among alcohol and drug (but not tobacco) use symptoms, which is related to worse prognosis and more severe psychopathology. Nevertheless, the central symptom (i.e., the one with most interactions with the other symptoms) within substance use disorders remained stable regardless of the stress level. In sum, the study suggests a quantitative, but not qualitative, difference in the relationship of alcohol and drug use symptoms associated with life stress.

Keywords: network analysis, symptom relationships, substance abuse, substance use disorder, NESARC

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Problematic substance use imposes large health and economic burdens on individuals, families, and society. The worldwide number of substance users is estimated at 2 billion, 1.3 billion, and 185 million for alcohol, tobacco, and drug consumption, respectively (World Health Organization, 2002). In 2000, substance use contributed to 55 million (12.4%) deaths worldwide and over 1 billion (8.9%) Disability Adjusted Life Years (i.e., life lost due to premature death or living with disability; Rehm, Taylor, & Room, 2006). Further, in the United States, problematic substance use has cost more than $740 billion annually, of which over $200 billion reflects health care costs (National Institute on Drug Abuse, 2017). Considering these significant impacts, an in-depth understanding of problematic substance use is an urgent public health need.

A growing body of evidence highlights the role of life stress in increasing vulnerability to substance use disorder (SUD; for a review, see Sinha, 2001). Major theories viewed stress as a precipitant of SUD. For example, the stress-coping model (Shiffman, 1982; Wills & Shiffman, 1985), tension-reduction model (Conger,

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The current study was based on de-identified open datasets—National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) I and II. The usage did not require IRT approval. The current findings have been presented at two conferences as a poster.

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1956), and self-medication model (Khantzian, 1987), all highlighted the use of substance as a (maladaptive) coping strategy in response to stress. Laboratory studies also showed increased substance consumption right after stress exposure (Higgins & Marlatt, 1975; Hull & Young, 1983; Marlatt, Kosturn, & Lang, 1975; Miller, Hersen, Eisler, & Hilsman, 1974; Pomerleau & Pomerleau, 1987). Neurologically, increased stress as well as substance consumption both lead to long-term neuro-sensitization in brain reward pathways, which is associated with substance craving, seeking behavior, and vulnerability to relapse (e.g., De Vries & Shippenberg, 2002; Kim et al., 2014; Le Dorze, Tassin, Chauveau, & Gisquet-Verrier, 2019; Robinson & Berridge, 1993). Overall, the initial use of a substance as a maladaptive response to stress is likely to be followed by exacerbated symptomatology of SUD.

Despite the behavioral and neurological understanding of the relationships among stress, substance consumption, and severity of SUD, less is known about the exact differences in symptomatology of SUD associated with stress. Greater *symptomatology* or *severity* are frequently used terms to stratify the level of psychopathology. Currently, based on the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM–5*; American Psychiatric Association, 2013), severity of SUD is defined by the number of symptoms. However, recent research in psychopathology has proposed that severity may not be an additive symptom effect. Further, interactions among symptoms can contribute to the onset, maintenance, relapse, and comorbidity of mental disorders (e.g., Borsboom & Cramer, 2013; Cramer, Waldorp, van der Maas, & Borsboom, 2010; Eaton, 2015; McNally et al., 2015). In light of this symptom-level approach, we wondered how stress would be associated with variation in relationships among substance use symptoms.

An effective way to quantify relationships among symptoms is to apply the network framework. On a theoretical level, mental disorders are hypothesized to be networks of symptoms interacting with and maintaining each other (e.g., Beard et al., 2016; Fried & Cramer, 2017; McNally, 2016; Steinley, Hoffman, Brusco, & Sher, 2017). Statistically, such hypothesized relations can be estimated using network psychometrics (Epskamp, Borsboom, & Fried, 2018). This framework has been successfully applied to a number of mental disorders, such as depression, generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), obsessive–compulsive disorder (OCD), and so on (for a review, see Fried et al., 2017). Furthermore, longitudinal studies have demonstrated that certain network characteristics, such as network centrality and connectivity, can predict the course and treatment outcomes of mental disorders (e.g., Boschloo, van Borkulo, Borsboom, & Schoevers, 2016; van Borkulo et al., 2015; van de Leemput et al., 2014). Although this framework is relatively young, it has gained considerable attention and recognition in the last few years.

To date, only a few studies have conducted network analyses of SUDs. Two studies investigated the comorbidity of alcohol use disorder (AUD) with posttraumatic stress disorder and other internalizing disorders (Afzali et al., 2017; Anker et al., 2017). Only one of the two was conducted at a symptom level, and neither of them included other types of SUDs. To our best knowledge, only one paper has included different types of SUDs and discussed them at a symptom level (Rhemtulla et al., 2016). However, to our knowledge, no previous study has investigated the association of life stress with network characteristics of substance use symptoms. Giving the significant role that life stress appears to play in the experience of SUDs, a symptom-level network of SUDs incorporating life stress would enhance our understanding of SUDs.

The Present Study and Hypotheses

To achieve a better understanding of stress-related variation in the symptomatology of SUD, the present study investigated the association of stress with variation in symptom manifestation and relationships in three major types of substance use disorders: alcohol, tobacco, and drug. We examined the prevalence rates of each substance use symptom in different stress level groups to identify stress-associated variation in symptom manifestation. Symptom relationships were estimated via network analysis. We compared two network characteristics—network structure and network connectivity—in different stress level groups to quantify the variation in symptom relationships associated with stress. In addition, to test stability and replicability of our findings, we repeated the analyses in a subsequent wave of data collection, in which the same participants were reassessed with the same interview approximately 3 years later.

Instead of identifying central symptoms for intervention, this study focused on patterns of differences in network characteristics associated with stress. The identification of central symptoms used to be a primary focus on network analysis, but recent research (e.g., Bringmann et al., 2019) has raised issues in interpreting the clinical importance of central symptoms in a psychological network, including the flow process (e.g., if a symptom is a cause or an effect) and node exchangeability (e.g., symptoms may cause different levels of impairment). Bringmann and colleagues further suggest focusing on the network dynamic as a whole. Thus, the current study minimized attention to the identification of central symptoms and investigated network-level characteristics associated with stress.

Given the exploratory nature of the current study, we could only derive limited hypotheses based on previous literature. As stress is shown to predict higher vulnerability to SUD (Sinha, 2001), we hypothesized stress would be positively associated with prevalence rates of all SUD symptoms; however, we were not able to predict the relationship between stress and the rank order of symptom prevalence. Second, as increased network connectivity was shown to predict worse prognosis of other mental disorders (e.g., van Borkulo et al., 2015), we predicted that we would observe greater network connectivity of substance use symptoms associated with stress. We did not have strong a priori hypotheses regarding which symptom relationship(s) would account for greater network connectivity, or the structural variance in symptoms network associated with stress.

Method

Participants

This study utilized data from the two waves of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Wave I was fielded in 2001–2002 (N = 43,903) with an 81% response rate. A Wave II follow-up was fielded in 2004–2005 (N = 34,653) with 86.7% of the eligible original sample

participating and a 70.2% cumulative response rate. The NESARC was a representative sample of the civilian noninstitutionalized U.S. adult population based on the 2000 Census. In Wave I, women composed 57% and the racial/ethnic composition was: White (56.9%), Black (19.1%), American Indian/Alaska Native (1.6%), Asian/Native Hawaiian/other Pacific Islander (3.1%), and Hispanic (19.3%). For detailed study design, see Grant and Dawson (2006).

Assessment

Substance use. Both Waves I and II assessed symptoms of alcohol/tobacco/drug use disorders occurring in the past 12 months based on the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV), a fully structured interview designed for lay interviewers. All the symptoms were measured dichotomously corresponding to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM–IV*; American Psychiatric Association, 1994). Symptoms of alcohol abuse/dependence, tobacco dependence, and drug abuse/dependence were examined separately. The test–retest reliabilities of AUDADIS-IV measures of substance use disorders are good to excellent (Grant, Dawson, et al., 2003; Ruan et al., 2008).

In the AUDADIS-IV, some of the symptom criteria were assessed by multiple questions. In this case, we recoded these questions as one binary symptom variable following the original coding rules in the AUDADIS-IV (Grant, Moore, Shepard, & Kaplan, 2003).

Life stress. The NESARC developed a list of stressful life events by adapting items from two existing measures: the List of Threatening Experiences (Brugha, Bebbington, Tennant, & Hurry, 1985) and the Schedule of Recent Events (Holmes & Rahe, 1967). The listed events were considered as common stressors that accounted for the majority of causes of stress in our daily life with similar severity. There was a consistent positive relationship between the number of past-year stressors and all measures of heavy drinking (Dawson, Grant, & Ruan, 2005).

The numbers of items in the list of stressful life events were not consistent across waves. There were 12 stressful life events assessed at Wave I; however, the researchers leading the NESARC made subtle changes in wording and divided "Did you or a family member have trouble with the police, get arrested or get sent to jail" into two questions, asking the participant and the family member separately, and changed "were you or a family member the victim of any type of crime" to "was something stolen from you" and "has anyone intentionally damaged or destroyed property owned by you." Wave II thus had 14 stressful life events.

As previous studies with the NESARC usually measured stress as a continuous variable based on the number of stressors in the past year and demonstrated significant and reliable findings regarding SUD (e.g., Dawson et al., 2005; Slopen, Williams, Fitzmaurice, & Gilman, 2011), we followed their method to create a new stress variable at each wave. As people with an extreme number of life stressors were rare, we combined individuals with seven or more stressors into one group. Therefore, individuals were divided into eight groups based on the number of stressors they had in the past year (range: 0–7+). Despite the subtle differences in items between waves, the percentage of people experiencing a certain number of stressors in the past year was similar across waves (see Table 1), warranting the comparison of results across waves.

Data Processing

We analyzed the complete sample of the NESARC instead of a restricted sample (e.g., nonabstainers or individuals meeting criteria for diagnosis) to avoid arbitrary clinical cut-off criteria and possible reduction in generalizability. Consequently, we replaced missing SUD symptom records of self-reported abstainers with zeros. To exclude the concern of possible artifacts due to zero imputation for abstainers, we: (a) conducted a set of sensitivity analyses comparing results from the full sample to those emerging in nonabstainers and individuals meeting criteria of diagnosis, and (b) estimated a modified network model on the full sample, increasing sensitivity to relationships among symptoms with low prevalence rates (i.e., low variance). For the detailed methods and results of these supplemental analyses, please see Sections S1 and S2 in the online supplementary materials. In short, although 69% of the full sample had data indicating no substance use symptoms, the pattern of symptom relationships (i.e., greater prevalence rates and correlations among symptoms associated with greater levels of stress) did not differ after we omitted abstainers or nonclinical

Table 1
Number of Individuals With Different Number of Past-Year Stressors Endorsing Past-Year SUD Symptoms in NESARC Waves I and II (Percentage in Parentheses)

Stressors	0	1	2	3	4	5	6	7+	NA
Wave I	10,243	8,449	7,343	3,860	2,024	1,197	628	535	374
Alc.	929 (9.07)	1,088 (12.88)	1,133 (15.4)	857 (22.2)	549 (27.12)	386 (32.35)	241 (38.38)	239 (44.67)	
Tob.	1,399 (13.66)	1,530 (18.11)	1,541 (20.99)	1,039 (26.92)	632 (31.23)	419 (35.00)	275 (43.79)	270 (50.47)	
Drug	66 (.64)	114 (1.35)	149 (2.03)	136 (3.52)	114 (5.63)	113 (9.44)	83 (13.22)	102 (19.07)	
Any	2,051 (20.02)	2,229 (26.38)	2,214 (30.15)	1,518 (39.33)	904 (44.66)	612 (51.13)	367 (58.44)	347 (64.86)	
Wave II	11,162	10,345	5,694	3,206	1,846	1,022	560	629	189
Alc.	1,144 (10.25)	1,436 (13.88)	1,042 (18.30)	769 (23.99)	531 (28.76)	322 (31.51)	202 (36.07)	266 (42.29)	
Tob.	1,617 (14.49)	1,878 (18.15)	1,349 (23.69)	849 (26.48)	621 (33.64)	361 (33.53)	234 (41.79)	295 (46.90)	
Drug	88 (.79)	165 (1.59)	179 (3.14)	166 (5.18)	134 (7.26)	115 (11.25)	86 (15.36)	129 (20.51)	
Any	2,415 (21.64)	2,843 (27.48)	1,983 (34.83)	1,305 (40.70)	857 (46.42)	509 (49.80)	319 (59.96)	397 (63.12)	

Note. Within-subject Pearson's r of stress levels = .36 and Kendall's τ = .24; N = 34,653. Alc = alcohol; Tob = tobacco; Any = any substance use symptoms; NA = missing values.

samples, which supported our analyses on the full sample. Further, the modified network model, where the sensitivity was increased, also suggested similar results overall, although it produced slightly lower R^2 values compared to the original network model, due to the trade-off between sensitivity and noise.

Associations of Life Stress With Prevalence Rates of Symptoms

To investigate the relationship of stress with prevalence of symptoms, we first calculated the unweighted prevalence rates of symptoms in each stress level group. Prevalence rates were "unweighted," which means we did not incorporate complex survey design (e.g., sampling weights, strata, and primary sampling units) into prevalence estimates, due to the current lack of network methodologies for complex design features. Hereafter, we refer to *unweighted prevalence rates* directly as *prevalence rates* for simplification and provide further discussion in the Limitations section.

Second, to examine the association of life stress on symptom prevalence rates in each network, we applied a bootstrapping method that matched the resampling procedure for network estimation (i.e., 1,000 bootstraps with 500 participants sampled at a time for each stress level and each type of substance). To quantify the association, we first aggregated the bootstrapped prevalence rates of different symptoms at different level of stress, and then applied a regression analysis on the aggregated data. We used the stress levels (range: 0−7+) as a predictor of prevalence rates and the symptoms as a categorical covariate; 95% confidence intervals of prevalence rates were also reported based on bootstrapping. Further, we examined the rank-order consistency of symptom prevalence rates across stress levels using Kendall's tau.

Association of Life Stress With the Symptom Networks

Symptom network estimation. In a symptom network, nodes and edges represent symptoms and the relationships among symptoms, respectively. We estimated separate symptom networks for the four different types of substance use problems (i.e., alcohol, tobacco, drug, and the consideration of these three substances simultaneously) for each of eight stress levels, resulting in ($4 \times 8 =$) 32 total networks. The tobacco use network contained seven nodes, because the NESARC only assessed tobacco dependence, but not abuse; networks for alcohol and drug use contained 11 nodes; and the multiple-substance network contained ($7 + 11 + 11 =$) 29 nodes.

We estimated Ising network models via the R package *IsingFit* (van Borkulo, Epskamp, & van Borkulo, 2016). The Ising model is the appropriate undirected network model for binary data (van Borkulo et al., 2014), in which nodes stand for binary variables and are connected by undirected edges indicating *conditional dependence*, which is the relationship between two nodes with the effect of other nodes removed. Nodes linked by edges with larger weights are more likely to appear together (Epskamp et al., 2018). To control for spurious relations, we used the "least absolute shrinkage and selection operator (LASSO)" with model selection based on the Extended Bayesian Information Criterion (EBIC; hyper-parameter $\gamma = 0.25$) to add a regularizing penalty, which shrinks all parameters and sets very weak (i.e., likely false positive) relations to exactly zero. In addition, we used the so-called "AND rule," where a coefficient was only estimated as nonzero in the network structure if both conditional dependence coefficients for a given edge (e.g., A predicting B AND B predicting A) were nonzero. This regularization returns a sparse/parsimonious network that is more interpretable and has been shown to perform well in retrieving known network structures in a validation study (van Borkulo et al., 2014).

Bootstrapping was used to (a) examine the stability of networks (Epskamp et al., 2018), and (b) enable comparison of networks with unequal sample sizes. We computed 1,000 bootstraps with 500 participants sampled at a time for each network representing the relationships among symptoms of a specific substance problem at a particular stress level.

The visualization of networks was based on the mean graph of 1,000 bootstraps and a modified version of the force-directed node placement developed by Fruchterman and Reingold (1991). To reduce visual interruptions from spurious edges, we excluded edges that occurred less than 50% of the time in the 1,000 bootstraps and only used the average weights of the remaining edges for visualization. The final layout represented the average strength of relationships among nodes across stress levels, where nodes with stronger relationships tended to be closer. Additionally, both thickness and saturation of edges were a direct representation of the degree of conditional dependence among nodes. The colors of edges referred to the sign of association: gray for positive and red for negative association.

Network structures. We used the Network Comparison Test (NCT; van Borkulo et al., 2017), a permutation based hypothesis test, to assess the *structural difference* among networks of different stress levels. The NCT allowed us to compare two networks containing the same nodes (i.e., substance use symptoms) of different subpopulations (i.e., individuals with different levels of stress) at a time (For detailed description of the NCT method, please see Section S3 in the online supplementary materials.) We conducted pairwise NCT comparison on networks across eight stress levels and reported the absolute value and significance level of structural difference between networks.

Network connectivity. Two network connectivity indices, namely *overall network strength* and *average dyadic efficiency* (Pasquaretta et al., 2014), were used to quantify network connectivity. The overall network strength is the sum of the actual weights of all edges in a network. The average dyadic efficiency is defined as the average of inverse shortest path lengths of each pair of nodes within a network. It indicates the information spreading speed within a network and is more sensitive to changes of global connectivity (e.g., the strengths of many edges increase slightly) than local ones (e.g., the strength of one edge increases drastically), whereas the overall network strength is equally sensitive to global or local changes as long as the total amount of weight changes is the same.

For each substance (i.e., alcohol, tobacco, drug, and the combination of the three), we regressed the connectivity indices on stress levels (range: 0–7+). Each level contained 1,000 data points of estimated network connectivity resulting from our bootstrapping approach. Because we have two indices and four different substance groupings, eight orthogonal polynomial regressions were conducted. We examined potential linear, quadratic, and cubic

effects. The R-squared value of each model and its 95% confidence interval (Algina & Olejnik, 2000; Lee, 1971) were reported. Due to a large number of data points of estimated network connectivity resulting from bootstrapping (1,000 bootstraps for each network), either the significant change of R^2 or common model selection criteria such as the Bayesian Information Criterion (BIC) would likely favor the higher order predictor (e.g., cubic effects are preferred over quadratic effects). Thus, instead of solely relying on quantitative indicators, we chose the best-fitting model based on the magnitude of change in R^2 (at least above 0.01) as well as the visualized trend of network connectivity over stress levels.

Cross-Time Replication

To examine the cross-time replicability of current findings, we repeated the Wave I analyses using past-year Wave II data. Only participants completing both waves ($N = 34{,}653$) were included in analyses, so we could better attribute differences of results between waves, if any, to time-variant components, without mixing them with individual variance.

Results

The number of individuals experiencing different numbers of past-year life stressors at Waves I and II, and the number of individuals endorsing different substance use symptoms within each group, are presented in Table 1. Most individuals encountered few life stressors in the past year. In addition, within each stress-level group, the number of individuals endorsing different types of substance use symptoms differed. More people endorsed tobacco use symptoms than alcohol use symptoms and more alcohol use symptoms than drug use symptoms.

While the size of each stress group and the number of individuals endorsing different substance use symptoms were similar across waves, group membership varied by time (within-subject Pearson's r of life stress levels = 0.36 and Kendall's $\tau = 0.24$). While membership tended to vary, the increasing pattern of prevalence and relationship (i.e., average correlation) of symptoms over stress groups of the full sample were highly similar between waves ($r_{\text{W1 vs. W2 prevalence}} = 0.995$, $r_{\text{W1 vs. W2 symptom relationship}} = 0.965$; for the details please see Section S1 in the online supplementary materials). In addition, network analyses of both waves returned highly similar results for each substance category. Due to this consistency, we only report the results for Wave II, where more participants experienced stress in the past year in the present paper; for a replication of the results in Wave I, please see Section S5 in the online supplementary materials.

Association of Life Stress With the Prevalence Rates of Symptoms

Visualization of the predictive effect of life stress on the prevalence rates of symptoms are presented in the right column of Figure 1. The absolute prevalence rates of all symptoms—regardless the type of substance—were associated with life stress; the average prevalence rates of symptoms could be well predicted by stress levels: For every additional stressor a group had, we anticipated the prevalence rate of alcohol, tobacco, drug, and combined substances symptoms to increase by 0.9% ($p_{\text{alc}} < 0.001$, $R^2_{\text{alc}} = 0.638$), 0.14% ($p_{\text{tob}} < 0.001$, $R^2_{\text{tob}} = 0.585$), 0.5% ($p_{\text{drug}} < 0.001$, $R^2_{\text{drug}} = 0.739$), and 0.9% ($p_{\text{all}} < 0.001$, $R^2_{\text{all}} = 0.476$), respectively. Although symptom prevalence rates were significantly and positively associated with stress, the rank order of symptom prevalence rate remained stable across stress levels. The lowest Kendall's τ among symptoms across stress levels was 0.792 (for the detailed values, please see Table S4 in the online supplementary materials). In sum, life stress was not associated with the rank order of prevalence rates among substance use symptoms but was well associated with the absolute prevalence rates—regardless of substance type.

Association of Life Stress With the Symptom Networks

Estimation of symptom networks. The symptom networks of four types of substances (alcohol, tobacco, drug, and the substances combined), each in eight different stress level groups, are presented in Figure 1. Each network depicted the mean network across bootstraps. In the alcohol and drug use symptom networks, the connections among symptoms were positively associated with stress, whereas such a phenomenon was less obvious in the tobacco use symptom network. In the combined substances network, reliable connection (i.e., the edge observed in over 50% of the bootstraps) between drug and alcohol use symptoms only appeared in the population encountering more than five stressors in the past year, while there was no reliable connection of tobacco with alcohol or drug use symptoms in any stress level group.

Network structures. We conducted pairwise network structural invariance tests for networks of the same substance use symptoms at different stress levels. The results showed no significant structural difference between any two observed networks (for the absolute degrees and significance levels of structural differences among networks, please see Table S5 in the online supplementary materials). Therefore, the null hypothesis of structural invariance could not be rejected, indicating that network structures was not significantly associated with life stress.

Network connectivity. For each of the 32 networks (see Figure 1), we estimated overall connective strength and average dyadic efficiency, averaged over 1,000 bootstraps. The estimated values are presented in Figure 2. The orthogonal polynomial regression lines deemed optimal from change in R^2 and visual inspection are given in Table 2 and Figure 2.

The magnitude and pattern (i.e., linear, quadratic, or cubic) of association between life stress and symptom network connectivity differed by the type of substance. For the alcohol use network, the positive associations of network strength and efficiency with the levels of stress could be well explained by a quadratic model. In terms of tobacco, the R^2 values were small in all models, indicating the connectivity of tobacco use symptoms was not associated with the levels of stress. For the drug and combined substance use networks, the cubic model could better explain the positive associations of network strength and efficiency with the levels of stress. In addition, in all cases but tobacco use symptoms, the correlations between strength and efficiency were above .95 ($r_{\text{alc}} = 0.953$, $r_{\text{tob}} = 0.745$, $r_{\text{drug}} = 0.989$, $r_{\text{all}} = 0.981$), indicating a global positive relationship between network connectivity and the levels of stress. In sum, life stress had strong nonlinear asso-

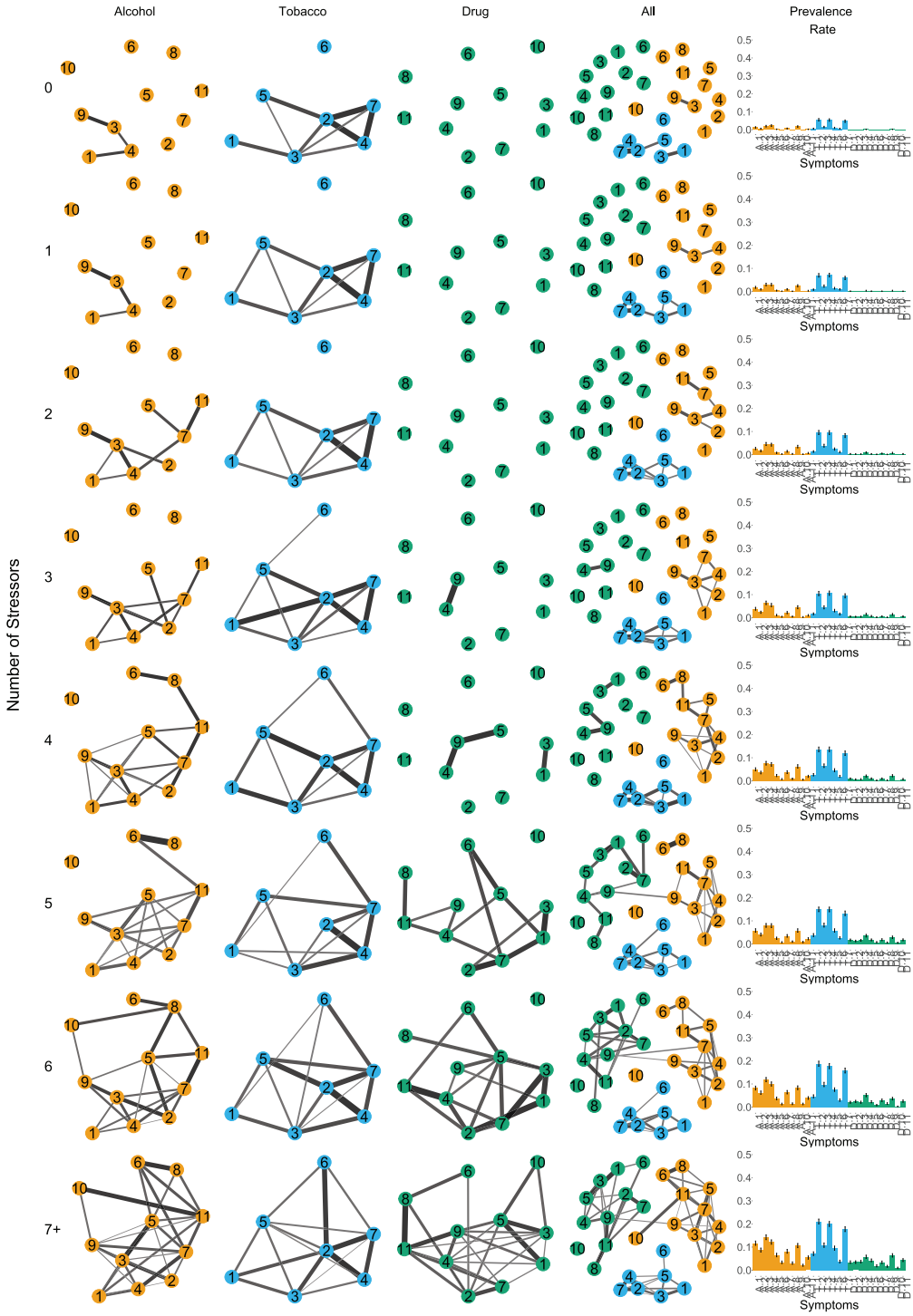

Figure 1. Symptom networks and prevalence rates of different substance use problems across stress levels (Wave II). Nodes = symptoms; thickness of edges = degree of condition dependence; number of nodes: 1 = tolerance, 2 = withdrawal, 3 = larger amount/longer duration than intention, 4 = failing to cut down despite efforts, 5 = spending lots of time, 6 = giving up/reducing other daily activities, 7 = continued using despite knowledge, 8 = failure to fulfill major role, 9 = physically hazardous, 10 = legal problems, and 11 = social and interpersonal problems. See the online article for the color version of this figure.

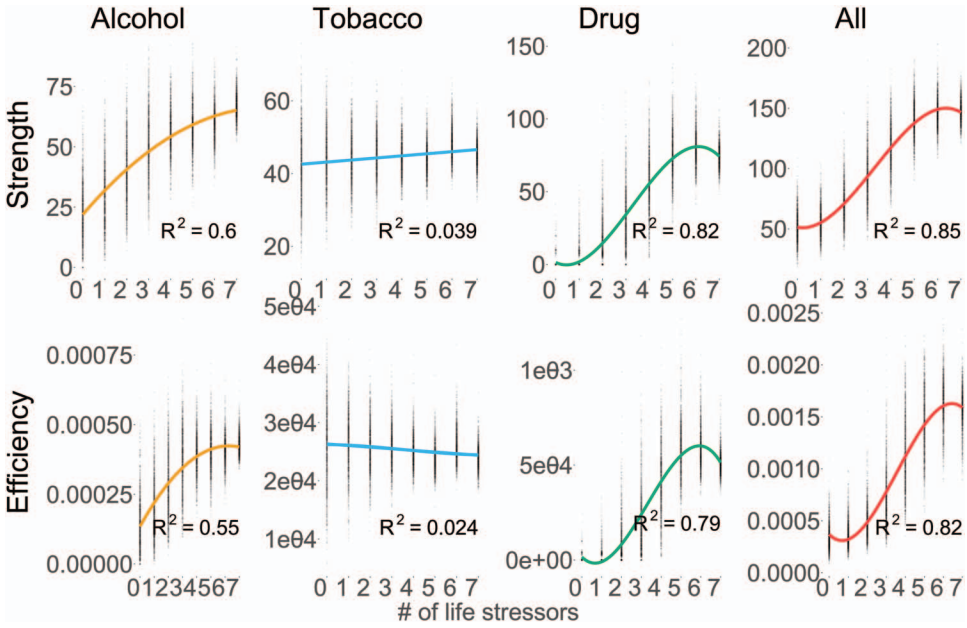

Figure 2. Regression of network connectivity on life stress (Wave II). See the online article for the color version of this figure.

ciation with network connectivity of alcohol, drug, and combined substance use.

Cross-Time Replicability

The replicability of network analysis results has become a topic of great interest in recent years (Borsboom et al., 2017; Epskamp et al., 2018; Forbes, Wright, Markon, & Krueger, 2017; Fried et al., 2018; Fried & Cramer, 2017; Steinley et al., 2017). To those ends, we took three approaches to evaluate the extent to which our findings might be replicable. First, we replicated the same analysis in two waves of the NESARC and demonstrated similar findings. Second, we used bootstrap methods to evaluate the stability and accuracy of our parameter estimates and results. Third, we moved beyond simply seeking central nodes by looking at the patterns of differnces in network characteristics (e.g., connectivity and structure) over eight subgroups based on stress. While this approach does not rule out the possibility that an independent dataset of new participants might produce different findings, it does suggest that our results were replicable across two unique assessments occurring nearly 3 years apart. In sum, these three approaches demonstrated no evidence that our findings are not replicable but, like all science, require replication in independent samples by independent teams of researchers.

Table 2
R^2 Values and 95% CIs of Different Models—Wave II

Substance	Linear	Quadratic	Cubic
		Strength	
Alcohol	.6 [.59, .61]	.63 [.62, .64]	.63 [.62, .64]
Tobacco	.04 [.03, .05]	.04 [.03, .05]	.04 [.03, .05]
Drug	.76 [.76, .77]	.77 [.76, .78]	.82 [.82, .83]
All	.82 [.81, .82]	.82 [.82, .83]	.85 [.85, .86]
		Efficiency	
Alcohol	.49 [.48, .5]	.55 [.54, .56]	.55 [.54, .56]
Tobacco	.02 [.02, .03]	.02 [.02, .03]	.02 [.02, .03]
Drug	.71 [.7, .72]	.72 [.71, .72]	.79 [.79, .8]
All	.77 [.77, .78]	.77 [.77, .78]	.82 [.81, .82]

Note. Underlined values indicate R^2 values of the optimal models.

Discussion

To our knowledge, this is the first study to investigate the association between stress and variation in symptomatology of SUD via network analysis. Life stress was associated with greater prevalence rates of all types of substance use symptoms and greater connectivity of alcohol, drug, and combined substances symptom networks, but not connectivity of the tobacco symptom network. In addition, life stress was associated with neither rank-order stability of prevalence rates nor network structures of all types of substance use symptoms.

Tobacco Use Symptom Network as an Exception to Greater Network Connectivity

The greater network connectivity associated with stress that appeared in all types of substance other than tobacco use symptoms could be due to at least two reasons. First, measurement differences between tobacco and other types of substances use symptoms may be a confounding variable. In the NESARC, a wider range of symptoms was assessed for alcohol and drug use disorders than for tobacco use disorder. The symptoms that used to be labeled as nicotine abuse in prior versions of the *DSM* were not assessed. While it is possible that adding tobacco abuse symptoms would change network connectivity at different stress levels, it is worth pointing out that the greater network connectivity at higher

stress levels in other substances was not due to greater connections specifically among (previously labeled) substance abuse symptoms.

Second, as the connectivity of tobacco dependence symptoms remained high regardless of stress level, there may be a ceiling effect. Unlike illicit drugs, tobacco and alcohol are commercially accessible. Further, tobacco leads to stronger psychological and physical dependence compared to alcohol (Nutt, King, Saulsbury, & Blakemore, 2007). Higher accessibility combining with stronger addictiveness may result in the observed ceiling effect—high network connectivity of tobacco use symptoms even in low stress-level groups.

Local Versus Global and Nonlinear Positive Associations With Network Connectivity

We used two indicators, *overall network strength* and *average dyadic efficiency*, to indicate local and global network connectivity, respectively. As the two indicators behaved in a similar pattern, our results support positive associations of stress with overall connections among symptoms without exceptional cases. In other words, the greater network connectivity in higher stress-level groups was not due to relationships among a specific group of symptoms, but the overall relationship among all symptoms. Further, as the greater network connectivity of the combined-substance use network was not only due to local connections among specific symptoms (i.e., greater network connectivity among the same kind of substance use symptoms), but instead to global ones, this indicates an greater risk of polysubstance use disorder associated with stress.

The greater network connectivity of different substance use symptoms as a function of stress was not linear. For alcohol, drug, and combined substance use symptoms, the positive slope of connectivity on stress reached a plateau after six stressors, indicating a ceiling of connectivity among substance use symptoms. In addition, network connectivity remained close to zero in drug use symptoms before the number of stressors reached two. This floor effect may result from heterogeneity of symptoms within the limited sample endorsing drug use symptoms in low-stress groups. Although we may be inclined to identify the critical points of a slope (e.g., at what level of stress does the network connectivity reach a plateau), the critical points shown in the current study should not be overinterpreted, because they are subject to differences in stress measurement and individual differences. Therefore, in the following discussion, we mainly focus on interpreting the global linear positive associations with network connectivity shared by alcohol, drug, and combined substance use symptoms.

Possible Interpretations of the Global Positive Linear Associations With Network Connectivity

The global positive linear associations between network connectivity and stress can be interpreted in several ways. A first interpretation is that symptoms and stress interact with each other, manifesting as greater network connectivity associated with stress. Symptoms of SUD in *DSM–IV* (American Psychiatric Association, 1994) included increased substance consumption, cognitive symptoms, physical or psychological addiction, and psychosocial impairments. Although most studies focused on the increased substance consumption and neurological changes in stressful situations (Sinha, 2001) and viewed symptom criteria of SUD as additive indicators of severity, the interactions among symptoms and stress are plausible. Stress may not only lead to increasing substance use but also intensify interactions among substance use symptoms. Further, symptoms of psychosocial impairment can result in profound stress and trigger another vicious cycle.

A second possibility is that there is an unobserved third variable that impacts both stress and substance use symptoms simultaneously, which would appear in our analyses as a direct association between the two. One such possible candidate is socioeconomic status (SES). SES is associated with a variety of coping resources, including but not limited to financial, health, and social support (Almeida, Molnar, Kawachi, & Subramanian, 2009; Smith, 2004). These coping resources predict prognosis and remission of SUD (Moos, 2007; Moos & Moos, 2007). Although few studies were conducted at a symptom level, it is likely that the symptoms of SUD may correlate/interact more strongly in low-SES participants, due to a comparative lack of coping resources to stop a vicious cycle. On the other hand, negative life events also occur more frequently in low-SES group (Hatch & Dohrenwend, 2007). Overall, socioeconomic context may plan an important role as a third variable in our findings. Given the current research design, we are not able to rule out the influence of third variables; however, considering the well-documented behavioral and neurological interactions between stress and substance use problems (Sinha, 2001), it is worth investigating the direct interactions among stress and SUD symptoms in a longitudinal design while controlling for potential third variables.

Limitations and Future Research

This study has several limitations. First, we did not incorporate complex design features of the NESARC due to the lack of established methods to do so for network models. As such, this sample should not be considered truly representative of the 2000 Census age, gender, and race/ethnic distributions of the United States; rather, our results should be viewed as those emerging from analysis of a large national survey with a diverse group of participants and with generalizability likely superior to that of smaller or convenience samples.

Second, while NESARC is the largest psychiatric epidemiological study of U.S. adults, it was designed to assess SUDs in the general population Individuals with more severe SUDs were less likely to be included (e.g., inpatient samples), and the majority of the sample did not have diagnoses of SUDs. Therefore, our model may not best illustrate the relationship among stress and extremely severe SUD symptoms. The generalizability of the current study is likely superior to that of smaller clinical samples, although replication studies with clinical samples are necessary to apply the current inferences to populations with more severe SUDs.

Third, the AUDADIS-IV used in the NESARC we analyzed is based on the *DSM–IV* rather than *DSM–5*. Therefore, new symptom criteria of SUDs, such as "craving, or a strong desire, or urge to use substances" (APA, 2013) is not included in the current study. In addition, the NESARC did not assess tobacco abuse, but only tobacco dependence, and we therefore did not have information regarding other tobacco use symptoms. Fourth, while we replicated our findings in two waves of data, these data were

collected from the same participants. Although this reduced concerns about replicability of our findings somewhat, replication studies with independent samples are necessary.

Fourth, the construct of stress lacks a uniformly accepted definition, which leaves questions regarding best measurement practices (for a review, see Monroe, 2008). Some researchers emphasized individual cognitive appraisal of stress, which renders stress as a subjective personal experience (Lazarus & Folkman, 1984), while others emphasized the evolutionary functions and the biomarkers of stress (Nesse, Bhatnagar, & Ellis, 2016). Some researchers have criticized the term *stress* as having ascended to a level of abstraction and ambiguity with limited usefulness and therefore reemphasized the importance to consider the general effect of a particular event to a particular population (Kagan, 2016). As the NESARC only assessed the occurrence of common stressful events in the past year, we could only approach the concept of stress in one dimension similar to Kagan's proposition. Future studies are suggested to incorporate multifaceted assessment for stress to control for individual differences in perceived severity of stress.

Lastly, as the current study was a between-subjects study conducted in cross-sectional data, the directions of interactions among the symptoms remained unknown. Causal relationships among symptoms serve as important information especially for clinical interventions. Individual differences may also occur in the causal chain of symptoms. Future studies are suggested to identify specific subgroups based on the pattern of causal chains through Ecological Momentary Assessment (EMA; Bos, Schoevers, & aan het Rot, 2015; Wichers, 2014) and to conduct clinical trials to investigate treatment efficacy for different subgroups.

Summary

To our knowledge, this is the first study to investigate the variation of symptomatology in SUDs associated with life stress via a network approach. Our results suggest that life stress is positively associated with elevated prevalence rates of all substance use symptoms and greater symptom connectivity of alcohol, drug, and polysubstance. However, the rank order of symptom prevalence and network structure are not significantly associated with stress. Further studies are required to disentangle the complicated dynamic between stress and substance use symptoms and to examine the possible impact of life stress on the effectiveness of addiction interventions for potential subgroups.

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