Mood Symptoms and Impairment Due to Substance Use:

A Network Perspective on Comorbidity

Daniel P. Moriarity¹, Corinne P. Bart¹, Allison Stumper¹, Payton Jones², Lauren B. Alloy¹

¹Department of Psychology, Temple University

²Department of Psychology, Harvard University

Correspondence concerning this article should be addressed to Lauren B. Alloy,
Department of Psychology, Temple University, Weiss Hall, 1701 N. 13th St., Philadelphia, PA 19122, United States of America. Fax: 1-215-204-5539. E-mail: lalloy@temple.edu.

Funding: This research was supported by National Institute of Mental Health Grants MH077908 and MH102310 to Lauren B. Alloy and by funding from the Civic Foundation via the Rosalyn and Stephen Weinstein Summer Graduate Research Award to Daniel P. Moriarity.

Declarations of interest: none
Mood disorders and problematic substance use are highly comorbid and confer reciprocal risk for each other. Despite many theories about comorbidity positing that specific features of one disorder pose risk for the other, there is a dearth of studies utilizing analytic approaches that correspond to this theory. A sample of 445 participants (59.8% female, Mage = 20.32 years) completed measures of depression symptoms, hypo/mania symptoms, and impairment due to substance use. Prospective models found that interpersonal impairment due to substance use was the strongest predictor of future mood symptoms and suicidal ideation was the mood symptom most predictive of substance-related impairment. Further, intrapersonal impairment due to substance use was the domain of impairment most predicted by past mood symptoms (specifically depression) and irritability was the mood symptom most predicted by past substance-related impairment. Results support different inputs/outputs for reciprocal risk conferred by mood symptoms and problematic substance use.
Introduction

Mood disorders (unipolar depression [UD] and bipolar spectrum disorders [BSDs]) and problematic substance use frequently are comorbid (Kessler et al., 1997). This co-occurrence is associated with numerous negative consequences including worse treatment outcomes, more severe course of illness, and heightened risk of suicide (Tolliver & Anton, 2015). In fact, compared to individuals with no mood disorders, individuals with UD were approximately twice as likely, and people with a BSD nearly seven times as likely, to have a history of substance use disorder (Kessler et al., 1997). Importantly, research suggests that the relationship between problematic substance use and mood symptoms is bidirectional in nature (Pacek, Martins, & Crum, 2013; Salloum & Thase, 2000). This is consistent with theories that suggest that one reason for this comorbidity is that features of one disorder increase risk for the other (see Strakowski & DelBello, 2000 for a review). Intuitively, and in line with recent research suggesting that not all symptoms of a given diagnosis (e.g., depression) have the same risk factors (Fried, Nesse, Zivin, Guille, & Sen, 2014), it is possible that not all mood symptoms confer equal risk for all types of substance use-related impairment, and vice-versa. To explore this possibility, the present project employed network analyses with cross-sectional and longitudinal data to investigate the interplay between symptoms of depression, hypomania/mania (henceforth referred to as hypo/mania), and impairment due to substance use.

Mood Symptoms and Substance Use: Reciprocal Risk

Epidemiological findings consistently indicate that mood and substance use disorders are highly comorbid; however, there is limited prospective studies investigating the role of each disorder as reciprocal causal risk factors for the others. Some evidence suggests that adolescent
onset of substance use disorders significantly increases risk for developing a mood disorder, particularly BSD (Kenneson, Funderburk, & Maisto, 2013), whereas other work in adult samples has found that depression can be both a risk factor and consequence of substance use disorders (Kessler et al., 2005). A number of theories linking mood disorders and substance use disorders as risk factors for one another exist. For example, substance use may be a way for individuals to cope with negative affect and attenuate their dysphoria, whereas problematic substance use may lead to depression during the withdrawal syndrome or as a result of substance use-related impairment (e.g., interpersonal) that could trigger depressive symptoms such as depressed mood and negative self-concept (Kessler, 2004; Markou & Kenny, 2002; Rappeneau & Bérod, 2017; Swendsen et al., 2010). On the opposite side of the mood spectrum, the impulsivity and reward hypersensitivity associated with hypo/manic episodes could lead to engaging in risky behaviors with rewarding properties such as substance use. Additionally, a history of substance use is associated with earlier onset of bipolar disorder and has been hypothesized to be a potential trigger for individuals with pre-existing vulnerabilities to BSDs, potentially via social and/or biological substance-related consequences (e.g., interpersonal difficulties, social/circadian rhythm dysregulation, neural adaptations to the substance, etc.; Cardoso et al., 2016; see Strakowski & Delbello, 2000 for review).

An examination of more specific factors that may contribute to the potential reciprocal risk between mood and substance use disorders is warranted. For example, the cumulative failure model posits that specific negative outcomes related to substance use engagement (i.e., failure in social and academic/work domains) lead to subsequent depression by undermining an individual’s confidence in their abilities (Patterson & Stoolmiller, 1991). In a similar vein, substance use (particularly among adolescents) may impair normal brain development, and thus,
lead to cognitive impairment, which precedes mood symptoms (Peeters, Vollebergh, Wiers, & Field, 2014). For example, the associations of bipolar disorder with decreased cortical gray matter volumes and neurocognitive impairment may be exacerbated by the effects of substances of abuse on neurodevelopmental processes (Balanzá-Martínez, Crespo-Facorro, González-Pinto, & Vieta, 2015). It is notable that most of these theories do not focus on the frequency of substance use as a risk factor, rather, risk is conferred by the difficulties that result from problematic substance use. On the other hand, pre-existing mood symptoms may predict subsequent problematic substance use via difficulties in peer relationships (including irritability and peer deviance), and substance use may emerge as a way to cope with interpersonal distress (Hussong, Jones, Stein, Baucom, & Boeding, 2011). Indeed, there is evidence that depression symptoms associated with difficulties in social adjustment and poor coping skills are most predictive of engaging in substance use (Sanchez et al., 2015; Thornton et al., 2012). Another potential explanation is that individuals with extreme low or high affect might use substances as a means to regulate or amplify that affect, respectively (Blum et al., 2000; Bowirrat & Oscar-Berman, 2005; Volkow, Fowler, & Wang, 2003). Further, some symptoms of hypo/mania (e.g., decreased need for sleep and increased activity) might increase risk for engaging in problematic substance use by increasing risk for exposure to alcohol and drugs at parties, bars, etc. This evidence suggests that the relationship between mood symptoms and substance use impairment might be conceptualized more accurately at the element level (e.g., symptom/domain of impairment), rather than diagnostic level.

**Network Theory of Comorbidity**

Investigation of comorbidity at the element level has the possibility to inform the etiological and nosological understanding of the comorbidity of mood symptoms and
problematic substance use. Specifically, recent advances in network science allow for a nuanced investigation of the relationships between these phenomena. Contrary to the more traditional common-cause conceptualization of psychopathology, network theory argues that symptoms are not all the result of a single latent factor. Rather, symptom co-occurrence may reflect symptom-to-symptom relationships, a perspective seen in several theoretical models of comorbidity (e.g., Strakowski & DelBello, 2000). When applied transdiagnostically across both mood symptoms and problematic substance use, this perspective has the potential to test the theories described above and improve our understanding of the nature of comorbidity (see Cramer, Waldorp, van der Maas, & Borsboom, 2010 for a theoretical paper regarding the application of network theory to comorbidity).

Scholars have debated the relative merits of a network approach (Forbes, Wright, Markon, & Krueger, 2017, see Borsboom et al., 2017 for a response). One potential benefit is that it enables element-wise (e.g., symptom-level, specific domain of impairment level) investigations of psychopathology. This facilitates transdiagnostic research in that, unless a researcher specifies otherwise (e.g., calculating bridge centrality, described below), network models treat all variables as separate entities, encouraging interpretations at the level of the behavior/cognition/symptom rather than at the level of the diagnostic category.

**The Present Study**

Although the theory that some features of mood disorders might increase risk for problematic substance use, and vice-versa, is not new, recent advances in network modeling allow for unprecedented tests of this theory. Using network analysis, this study simultaneously modeled relationships between five distinct domains of substance-related impairment (interpersonal, intrapersonal, social, impulsive, physical) and thirteen mood symptoms from both
ends of the mood spectrum (depression and hypo/mania) using contemporaneous and prospective models. This approach allowed for exploration of which mood symptoms are most strongly related to specific domains of substance-related impairment, and vice-versa. In particular, identification of central symptoms (e.g., symptoms with high expected influence, in/out prediction, described below) might highlight potential treatment targets or elements specifically likely to predict, or be predicted by, symptoms of the other disorder (Elliott, Jones, & Schmidt, 2019).

In order to elucidate the interplay between mood symptoms and domains of impairment from substance use, the current project addressed the following questions: 1) Do discrete domains of substance-related impairment have differential concurrent relationships with specific mood symptoms?; 2) Which specific mood symptoms most strongly predict future domains of substance use-related impairment, and vice-versa (i.e., out-prediction)?; and 3) Which specific mood symptoms are most strongly predicted by past substance use-related impairment, and vice-versa (i.e., in-prediction)?

**Methods**

**Participants and Procedures**

Participants in this study were drawn from the Teen Emotion and Motivation (TEAM) Project (Alloy et al., 2012), a recently completed prospective, longitudinal study investigating predictors of the onset and course of BSDs. Participants were selected via a two-phase screening procedure from the greater Philadelphia area (Alloy et al., 2012). In Phase I, 9,991 students aged 14-19 were recruited from 13 Philadelphia public high schools and two local universities. They completed two self-report trait measures of reward sensitivity: the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) Scales (Carver & White, 1994) and Sensitivity to
Punishment/Sensitivity to Reward Questionnaire (SPSRQ; Torrubia, Ávila, Moltó, & Caseras, 2001). Students who scored in the top 15th percentile on both the BAS-Total (BAS-T) of the BIS/BAS and the Sensitivity to Reward Scale (SR) of the SPSRQ composed the high BAS (high reward sensitivity) group (N=776), and those who scored between the 40th and 60th percentiles on both of these measures composed the moderate BAS (moderate reward sensitivity) group (N=404) of the main study sample. Participants with low BAS sensitivity were excluded because low BAS sensitivity is associated with vulnerability to unipolar depression (Depue & Iacono, 1989) and a major aim of Project TEAM was to examine vulnerability to first onset of BSDs based on the BAS/reward hypersensitivity model of BSDs. The screening sample was representative of adolescents ages 14-19 in the Philadelphia area on race, sex, and age (Alloy et al., 2012).

Participants who scored high BAS or moderate BAS on both the BAS-T and the SR were invited to a Phase II screening and were administered an expanded Schedule for Affective Disorders and Schizophrenia—Lifetime diagnostic interview (Alloy et al., 2008; Endicott & Spitzer, 1978) by interviewers blind to participants’ BAS risk group status; 244 high BAS and 146 moderate BAS participants were interviewed in Phase II. The exp-SADS-L interview was expanded to allow for generation of both DSM-IV-TR (American Psychiatric Association, 2000) and Research Diagnostic Criteria (RDC; Endicott & Spitzer, 1978) diagnoses. Participants were excluded from the final Project TEAM sample if they met DSM-IV-TR and/or RDC criteria for a lifetime history of any BSD, hypomanic episode, or psychotic disorder prior to the date of the BAS screening or were not fluent in English. Participants were included if they had a prior history of a DSM-IV-TR and/or RDC depressive episode.
Participants completed measures of impairment due to substance use, symptoms of depression, and symptoms of hypo/mania at Time 1 (T1) and Time 2 (T2; average months apart = 10.7, SD = 8.2). The analytic sample included 445 Project TEAM participants (281 high BAS and 164 moderate BAS, 99 with a history of a bipolar spectrum disorder) aged approximately 20.3 years at T1 (SD = 1.7 years). The sample was 59.8% female, 60.9% White, 21.5% Black, 10.1% Asian, 3.4% Latino, 2.7% Multiracial, and 0.2% Native American; 1.8% of the sample chose not to report their race. The sample of 336 participants with complete follow-up measures at T2 did not differ from the T1 sample on BAS group, race, or gender (ps = .99, .20, and .79, respectively).

Measures

Depression symptoms. Depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II; Beck, Brown, & Steer, 1996). The BDI-II is a 21-item measure assessing depressive symptoms in the past 30 days. Items are rated on a scale of 0-3, with higher scores indicating more severe symptoms. It has shown acceptable psychometric properties (Beck et al., 1996). The mean BDI-II score at T1 was 5.43, SD = 6.25. Due to power constraints, eight items closely matching eight DSM-5 depression criteria were included in this project: items 1 (sadness), 4 (anhedonia), 5 (guilt), 9 (suicidal ideation), 11 (irritability), 13 (indecisiveness), 17 (fatigue), and 18 (decrease in appetite). The BDI-II lacks an item measuring psychomotor retardation/agitation, so this symptom was not modeled. Additionally, decrease in sleep was not modeled as a depression symptom because a similar item was included in the hypo/mania measure and increased need for sleep was not measured on the BDI-II.

As several of the DSM-5 criteria for depression are multi-faceted (e.g., anhedonia can be either the loss of interest and/or pleasure) and measured by several items on the BDI, we used the
following rationale when selecting individual items: Item 4 was chosen for anhedonia because it
measures dissatisfaction globally whereas Items 12 and 21 specifically measure loss of interest in
people and sex, respectively. Increase/decrease in both appetite and weight are a single symptom
in the DSM-5, but the BDI-II only measures decreases in appetite and increases in weight. Item
18 (appetite) was chosen because weight increase is more likely to be secondary to other factors
(e.g., increase in appetite, changes in diet, decrease in activity). Feelings of guilt and
worthlessness make up the same DSM-5 criterion, but feelings of guilt (Item 5) was chosen over
other items relating to negative self-concept because it most clearly measured one of these two
criteria.

**Hypo/mania symptoms.** Symptoms of hypo/mania were assessed using the Altman Self-
Rating Mania Scale (ASRM; Altman, Hedeker, Peterson, & Davis, 1997). The ASRM consists of
5 items rated on a 5-point Likert scale (0-4), with higher scores indicating more severe
symptoms. The items assess the occurrence of five symptoms of hypo/mania over the past 30
days: inflated self-confidence, talkativeness, euphoria, reduced need for sleep, and increased
activity. Factor analyses have demonstrated that the five items load onto a single factor, and the
measure has demonstrated strong convergent validity with clinical interviews and other self-
report measures of hypo/mania (Altman, Hedeker, Peterson, & Davis, 2001). All five items were
used in analyses. The mean ASRM score at T1 was 4.77, $SD = 3.79$.

**Impairment due to substance use.** Impairment due to substance use was assessed using
the Short Inventory of Problems-Revised (SIP-R; Blanchard, Morgenstern, Morgan, & Labouvie,
2003). The SIP-R consists of 15 items that assess problems associated with drug and alcohol use
over the past 30 days (e.g., “My family has been hurt because of my drinking or drug use.”).
Items are rated on a 4-point Likert scale (1 = never, 2 = 1-2 times/month, 3 = twice a week, 4 =
daily/almost daily). The measure yields a total score and five subscales (interpersonal, intrapersonal, social role, impulsive, and physical) and has demonstrated good convergent validity (Kiluk, Dreifuss, Weiss, Morgenstern, & Carroll, 2013). The five subscales were used in the analyses. The means and standard deviations for the subscales at T1 were: interpersonal (M = 3.14, SD = .72), intrapersonal (M = 3.49, SD = 1.21), social role (M = 3.41, SD = .99), impulsive (M = 3.64, SD = .95), and physical (M = 3.42, SD = .97).

Statistical Analyses

Contemporaneous network estimation and expected influence. In network models, variables are referred to as “nodes”, and “edges” are associations between nodes controlling for all other nodes in the network (Epskamp & Fried, 2016). First, to explore cross-sectional associations among impairment due to substance use and symptoms of depression and hypo/mania, we estimated a Graphical Gaussian Model (GGM), using the R package qgraph (Epskamp, Schmittmann, & Borsboom, 2012). All five subscales of the SIP-R, all five items of the ASRM, and the eight BDI-II items listed above were included as nodes. All nodes were standardized to a 0-9 scale to avoid potential bias imposed by differences in node scaling. Further, because a number of items were heavily skewed and nodes included both continuous and ordinal variables, Spearman correlations were used to estimate the network (Epskamp & Fried, 2018).

To a) reduce the likelihood of false positive edges being included, and b) increase the sparseness of the graph and, thereby, interpretability, a graphical Least Absolute Shrinkage and Selection Operator (gLASSO) regularized the edge weights (Friedman, Hastie, & Tibshirani, 2010). This procedure biases all edge weight estimates towards zero and sets very small edge weights to exactly zero. The best fitting model was selected with the extended Bayesian
Information Criterion (EBIC) model selection procedure (Foygel & Drton, 2011). This procedure is implemented in the qgraph package (Epskamp et al., 2012), which was used to visualize the network structures. A modified Fruchterman-Reingold algorithm is used as part of the qgraph package to place more strongly connected nodes closer to each other, but the location of nodes should not be used to interpret properties of these nodes (Epskamp & Fried, 2018).

Stability and accuracy of edge weights were estimated via calculation of 95% confidence intervals (CIs) for all contemporaneous networks using non-parametric bootstrapping (1,000 bootstraps) in the R package bootnet (CRAN link: http://cran.r-project.org/package=bootnet). This approach does not test whether each edge is significantly different from zero. Rather, edges with CIs not inclusive of zero can be interpreted with confidence. Importantly, because gLASSO regularization biases all edge estimates towards zero, these sampling distributions are not centered on the true, unbiased, parameter value. Consequently, if the bootstrapped CIs include zero, it does not mean that the corresponding, unbiased CIs overlap with zero. However, if the bootstrapped CIs do not overlap with zero, it suggests that the corresponding, unbiased CIs do not overlap with zero (Epskamp, Borsboom, & Fried, 2018).

To quantify the total positive or negative connection each node had with the rest of the network in the contemporaneous model, we calculated one-step expected influence (EI), a measure of centrality that is the sum of edge weights directly attached to a node (Robinaugh, Millner, & McNally, 2016). Because the primary aim of this study was to explore how mood symptoms influence impairment due to substance use, and vice-versa, we also estimated one-step bridge expected influence using the bridge function of the R package networktools (Jones, 2018). Bridge EI quantifies the sum of the edge weights between a given node (e.g., a mood symptom) and all nodes from other constructs (e.g., a substance use impairment subscale). As the
focus of this study was the relationship between mood symptoms and substance use-related impairment, and not the relationship between depression and hypo/mania symptoms, all mood symptoms were categorized as one construct for the purposes of both the contemporaneous and temporal (described below) cross-construct analyses. In a scenario where edges represent causal connections, nodes with high bridge EI would be the most likely to influence other communities or be activated by nodes from a nearby community, and consequently, spread activation within its own community (Jones, Ma, & McNally, 2019). Before interpretation, it is necessary to test the stability of the centrality parameters using a case dropping procedure to test the proportion of the sample that can be dropped from the analysis and result in a .7 correlation between centrality estimates (i.e., expected influence) of the original sample and the new sample, resulting in a stability coefficient. A stability coefficient of .25 (25% of the sample dropped) is considered somewhat stable and at least .50 is considered stable. It is important to note that because these networks use cross-sectional data and are undirected, no interpretations of directionality can be made.

**Temporal networks.** We also examined cross-lagged panel networks of mood symptoms and impairment due to substance use at T1 and T2. To explore prospective associations between mood symptoms and substance use-related impairment, we computed a cross-lagged panel network (Rhemtulla, van Bork, & Cramer, 2018). This technique estimates the effects of nodes at T1 on all other nodes at T2, controlling for auto-regressive effects (i.e., regressing each variable at T2 on itself at T1). Following Rhemtulla et al. (2018), we first computed within- and between-timepoint coefficients and auto-regressive coefficients with regularized regressions. Penalized maximum likelihood with a LASSO penalty is applied to estimate a sparse network structure, similar to above. The glmnet package (Friedman et al., 2010) was used to calculate regressions
and the qgraph package (Epskamp et al., 2012) was used to plot all figures. We imposed identical maximum value of edge weights for both the contemporaneous and temporal networks to ease visual comparison. Cross-lagged (i.e., T1 to T2) edges are directed, meaning it is possible to estimate both in-prediction and out-prediction. In-prediction summarizes the proportion of variance for a given node at T2 that is accounted for by variables at T1. Out-prediction refers to the effect a given node at T1 has on variables at T2. Because the primary aim of this project was to explore the associations of mood symptoms on substance use-related impairment (e.g., the effect of mood symptoms at T1 predicting a given type of substance use-related impairment at T2), and vice versa, cross-construct effects were calculated, which exclude paths connecting nodes within the same community (e.g., the effect of mood symptoms at T1 predicting mood symptoms at T2).

Results

Contemporaneous Networks of Mood Symptoms and Impairment due to Substance Use

Figure 1 (top) presents the contemporaneous gLASSO network, which visualizes the regularized associations between eight depression symptoms, five hypo/mania symptoms, and the five subscales of impairment due to substance use. Bootstrapped correlation stability analyses found good stability for both edge weights and one-step expected influence (67% and 60%, respectively). Interestingly, there were no strong edges connecting hypo/mania symptoms and substance use-related impairment in this model. The nodes with the highest EI were sadness, indecisiveness, intrapersonal impairment, and elevated confidence (Figure 2).

When the effect of within-community edges (e.g., edges between a depressive or hypo/mania symptom with all other mood symptoms) was removed to calculate bridge EI, the patterns of centrality changed considerably. The domains of substance use-related impairment
with the highest bridge EI on concurrent mood symptoms were interpersonal impairment and impulsive impairment. The depression symptoms with the highest bridge EI on concurrent substance use-related impairment were sadness, guilt, and anhedonia (Figure 2). Because no symptoms of hypo/mania had edges connecting with domains of substance use-related impairment, they had no bridge EI.

**Temporal Networks**

Figure 1 (bottom) also shows the cross-lagged panel network. Edges represent cross-time effects and denote the direction of prediction with arrows. Figure 3 shows cross-construct (mood symptom $\rightarrow$ substance use impairment, substance use impairment $\rightarrow$ mood symptom) estimates of in-prediction and out-prediction (see Table 1). Substance use-related interpersonal impairment, and to a lesser extent, social role impairment, were the primary predictors of future mood symptoms. Conversely, suicidal ideation had, by far, the greatest out-prediction to future substance use-related impairment, followed to a lesser extent by guilt. Similar to the results of the contemporaneous networks, no hypo/mania symptoms predicted future substance use-related impairment.

In this sample, there were more cross-construct inputs compared to the outputs described above. Intrapersonal and physical substance use-related impairment were most strongly predicted by past mood symptoms. For depression, irritability, guilt, decrease in appetite, anhedonia, and indecisiveness had at least 1% variance predicted by previous substance use-related impairment.

For hypo/mania, only increased activity level had at least 1% variance predicted by previous substance use-related impairment.

**Discussion**
Mood disorders and problematic substance use confer risk for one another (Kessler et al., 2005), are frequently comorbid (Kessler et al., 1997), and their co-occurrence is associated with greatly elevated risk for additional negative outcomes (Tolliver & Anton, 2015). The current study extends previous research suggesting that discrete mood symptoms are differentially related to other risk factors, and that particular depressive symptoms are more strongly related to substance use-related impairment than others (Sanchez et al., 2015; Thornton et al., 2012) by using sophisticated network analysis and modeling symptoms from across the mood spectrum.

Specifically, 1) sadness, indecisiveness, intrapersonal impairment, and elevated confidence had the highest co-occurrence (indexed by expected influence) in the cross-sectional data; 2), when focusing on associations between mood symptoms and domains of substance-related impairment (indexed by bridge expected influence), interpersonal and impulsive impairment were the domains of impairment most strongly associated with mood symptoms, and sadness, guilt and anhedonia were the mood symptoms most strongly associated with impairment due to substance use. Prospective models found that 3) interpersonal impairment and social role impairment due to substance use were the primary predictors of future mood symptoms, but 4) intrapersonal and physical impairment were the domains of substance use-related impairment most strongly predicted by previous mood symptoms. Finally, 5) suicidal ideation and guilt were the mood symptoms that most strongly predicted future substance use-related impairment, but 6) irritability, guilt, and decrease in appetite were the mood symptoms most strongly predicted by previous substance use-related impairment. These results are discussed in the context of theory below.

**How Do Specific Mood Symptoms Concurrently Relate to Domains of Substance Use-related Impairment?**
Contemporaneous network models of mood symptoms and substance use-related impairment offer insight into the co-occurrence of mood symptoms and problematic substance use. Because these models used cross-sectional data, no interpretations regarding directionality can be made. Thus, the results from these models reflect element-wise patterns of symptom/substance use-related impairment co-occurrence. Across the entire network, nodes with the highest expected influence were sadness, indecisiveness, intrapersonal impairment, and elevated confidence. Notably, the nodes that were highly connected in general (high expected influence) were not the same nodes that showed high cross-domain connectivity (high bridge expected influence), suggesting that a different subset of constructs play the primary role in mood disorder/problematic substance use comorbidity. Bridge expected influence metrics highlighted that interpersonal and impulsive impairment were the domains of substance abuse most likely to co-occur with mood symptoms (specifically depression symptoms, because there were no edges between substance use-related impairment and hypo/mania symptoms). Sadness, guilt, and anhedonia were the depression symptoms that had the highest concordance with all domains of substance use-related impairment. Surprisingly, no hypo/manic symptoms had any expected influence on domains of substance use-related impairment (indeed, there were no non-zero edges between hypo/mania symptoms and impairment in this network).

**How Do Specific Mood Symptoms Predict Future Domains of Substance Use-related Impairment, and Vice-Versa?**

Temporal models provided interesting insight into how mood and substance use psychopathology bidirectionally confer risk for one another at the symptom/impairment domain level. Interpersonal and social role impairment were the primary substance-related predictors of future mood symptoms. This also is consistent with the cumulative failure model (Patterson &
Moriarty (1991), which posits that negative outcomes secondary to problematic substance use (e.g., interpersonal conflict, missing class or work) can lead to subsequent depression symptoms (which had stronger and more relationships to past substance use-related impairment than hypo/manic symptoms in this sample). Specifically, interpersonal substance-related impairment’s out-prediction had the greatest $R^2$ compared to the in- and out-prediction of the other nodes, highlighting interpersonal issues stemming from problematic substance use as a potentially important driver of mood symptoms in our sample.

Intrapersonal and physical impairment were the domains most associated with previous mood symptoms (specifically, depression symptoms, as hypo/manic symptoms had no cross-construct out-prediction in this sample). Conceptually, individuals who have negative self-concept (potentially using substances as a coping mechanism) and use substances to the point of impairment might internalize their problematic substance use as a reflection of their flaws (intrapersonal impairment). Further, depression is associated with changes in appetite and goal-oriented behavior (e.g., exercising) that might be exacerbated by problematic substance use (e.g., weight gain or loss, feeling hungover and missing planned exercise).

Among depression symptoms, suicidal ideation, and to a lesser degree, guilt, were the strongest predictors of future substance-use related impairment. As these symptoms are typically associated with negative self-concept, it is unsurprising that the domain of substance-related impairment most associated with previous depression was intrapersonal impairment. Taken into consideration with the large cross-construct in-prediction of intrapersonal impairment due to substance use, this study provides support for problematic substance use as a coping mechanism for suicidal ideation and guilt, which results in additional intrapersonal difficulties.
The finding that hypo/mania symptoms did not predict future substance-use related impairment in our sample suggests that depression symptoms present more risk for impairing substance use. However, it is worth repeating that our hypo/mania measure only included five symptoms, so there might be a stronger hypo/mania → impairing substance use association in a sample with a more thorough measure of hypo/mania symptoms or in a clinical sample.

Substance use-related impairment predicted some variation in all depression symptoms except fatigue and suicidal ideation. Specifically, irritability, guilt, and decreased appetite were the depression symptoms most strongly predicted by past substance use impairment. In contrast to the cross-sectional analyses and out-prediction estimates, two hypo/mania symptoms (increased levels of activity and increased confidence) were predicted by previous substance-use related impairment. However, it is worth noting that < 1% of the variability in self-confidence was accounted for by previous substance use-related impairment, limiting the substantive implications of this relationship. Importantly, although the irritability item was on the depression measure, irritability can be a symptom of both depression and hypo/mania. This is particularly interesting considering that it had the highest in-prediction of any of the mood symptoms in this sample. Further, the fact that more symptoms were predicted by past, rather than predicted future, substance use-related impairment might be evidence that only specific components of mood psychopathology increase risk for problematic substance use, whereas issues associated with problematic substance use might confer risk for mood symptoms more generally.

The notable differences in which nodes had the highest in- vs. out-prediction suggests that potential feedback loops may not be simplistic dyads, but instead may operate through a more complex pathway. Generally, mood symptoms (other than suicidal ideation and, to a lesser extent, guilt) largely seemed to operate as down-stream effects of, rather than risk factors for,
problematic substance use. Additionally, these differences highlight the importance of longitudinal data in network analyses to test for directionality.

Some of the results of the temporal models also dovetail with the contemporaneous models, highlighting the importance of network research utilizing both cross-sectional and longitudinal data. Interpersonal impairment had the highest bridge expected influence with mood symptoms (specifically depression, as there were no hypo/mania – substance use-related impairment edges in the contemporaneous networks) in the cross-sectional data and had the highest cross-construct out-prediction of the impairment domains. This highlights interpersonal impairment as highly comorbid with current depression symptoms as well as a risk factor for future depression symptoms. Additionally, anhedonia had some of the highest bridge expected influence of the depression symptoms in the cross-sectional data and had some cross-construct in-prediction from previous substance-use related impairment (albeit, small, at 1.3%). Guilt had a similar bridge expected influence in the contemporaneous models and had both cross-construct in-prediction and out-prediction from/to substance use-related impairment (granted, it had higher in-prediction value than out-prediction- 4.3 % vs 0.9 %) suggesting a bidirectional relationship in this comorbidity.

Strengths and Limitations

This study had several notable strengths. First, the sample was comprised of a large, diverse sample of late adolescents/young adults, a group at heightened risk for clinical levels of mood psychopathology and problematic substance use (Alloy et al., 2006; 2012; Hankin et al., 1998). Second, it includes a transdiagnostic approach to studying symptoms from both ends of the mood spectrum, maximizing the information about the psychopathological constructs studied and increasing relevance for both the etiology and nosology of the co-occurrence of mood and
substance use problems. Third, focusing on substance use-related impairment, rather than substance use itself, increases the clinical relevance of these findings. However, there might be additional information gained from examining substance use frequency, or predicting to use or impairment related to specific substances, which could be important future directions. Fourth, the inclusion of cross-sectional and longitudinal analyses maximizes the clarity of the information gained from the study.

Despite these strengths, results should be considered in light of several limitations. First, although we selected depression items based on DSM symptoms, there are a number of other symptoms measured by the BDI that might have been useful to include if we had a larger sample size. However, despite its breadth, the BDI did not include any items measuring psychomotor retardation or agitation. Additionally, the BDI is a much more thorough measure of depression symptoms than the ASRM is for hypo/mania symptoms. Future research should extend this study using a dataset that captures a wider range of hypo/mania symptomatology. Third, this sample was selected for high and moderate reward sensitivity. Whereas this increased the likelihood of recruiting participants with clinically relevant hypo/mania symptoms, it might reduce the generalizability of these results to individuals with low reward sensitivity, which also has been implicated in depression and problematic substance use etiology. Fourth, self-report measures might not be ideal for the constructs measured in this study because of risk for under-reporting (e.g., individuals experiencing hypomania might be less likely to report impairment due to substance use than euthymic or depressed individuals). Finally, although investigating these questions in a non-clinical sample selected for high and moderate reward sensitivity has benefits (described above), replication of these analyses in a clinical sample is an important next step.

Conclusion
Mood disorders and problematic substance use have extremely high rates of comorbidity (Kessler et al., 1997) and their co-occurrence predicts worse treatment outcomes, functional impairment, and increased risk of suicide (Tolliver & Anton, 2015). Consequently, elucidating the nature of the bidirectional association between these pathologies is an important public health concern. This project tested and found support for symptom/impaired domain-specific risk pathways in this comorbidity. Importantly, this project suggests that the components of these syndromes that predict risk for the other might not be the same components that are predicted by the presence of symptoms from the other disorder. Thus, the results from this study have implications for both the etiology and classification of mood disorder/problematic substance use comorbidity.
References


Fried, E. I., Nesse, R. M., Zivin, K., Guille, C., & Sen, S. (2014). Depression is more than the sum score of its parts: individual DSM symptoms have different risk factors. *Psychological Medicine, 44*, 2067–2076. https://doi.org/10.1017/S0033291713002900


Kenneson, A., Funderburk, J. S., & Maisto, S. A. (2013). Substance use disorders increase the

https://doi.org/10.1016/j.drugalcdep.2013.06.011


https://doi.org/10.1016/j.biopsych.2004.06.034


https://doi.org/10.1037/a0028445


https://doi.org/10.1016/j.jad.2012.11.059


Table 1. *Cross-construct In-prediction and Out-prediction Estimates*

<table>
<thead>
<tr>
<th>Node</th>
<th>In-prediction</th>
<th>Out-prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Interpersonal imp.</td>
<td>4.5 %</td>
<td>0.4 %</td>
</tr>
<tr>
<td>2. Social Role imp.</td>
<td>0.6 %</td>
<td>1.4 %</td>
</tr>
<tr>
<td>3. Impulsive imp.</td>
<td>0.0 %</td>
<td>0.3 %</td>
</tr>
<tr>
<td>4. Physical imp.</td>
<td>2.7 %</td>
<td>&lt; 0.1 %</td>
</tr>
<tr>
<td>5. Interpersonal imp.</td>
<td>0.1 %</td>
<td>9.8 %</td>
</tr>
<tr>
<td>6. Euphoria</td>
<td>0.0 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>7. Increased confidence</td>
<td>0.1 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>8. Decreased need for sleep</td>
<td>0.0 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>9. Talkativeness</td>
<td>0.0 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>10. Increased activity</td>
<td>1.1 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>11. Sadness</td>
<td>0.0 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>12. Anhedonia</td>
<td>1.3 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>13. Guilt</td>
<td>4.3 %</td>
<td>0.9 %</td>
</tr>
<tr>
<td>14. Suicidal ideation</td>
<td>0.0 %</td>
<td>8.1 %</td>
</tr>
<tr>
<td>15. Irritability</td>
<td>4.6 %</td>
<td>&lt; 0.1 %</td>
</tr>
<tr>
<td>16. Indecisiveness</td>
<td>1.3 %</td>
<td>&lt; 0.1 %</td>
</tr>
<tr>
<td>17. Increased fatigue</td>
<td>0.0 %</td>
<td>&lt; 0.1 %</td>
</tr>
<tr>
<td>18. Decreased appetite</td>
<td>3.1 %</td>
<td>0.0 %</td>
</tr>
</tbody>
</table>

Note: imp. = impairment
Figure 1. Contemporaneous (top) and cross-lagged (bottom) network of mood symptoms and impairment due to substance use.

Note: Green edges in the networks depict positive associations, red edges represent negative associations, and thicker/more saturated edges depict stronger associations. Circular paths are auto-regressive associations.
Figure 2: One-step expected influence (left) and one-step bridge expected influence (right).

Note: X-axis represents z-standardized scores.
Figure 3. Cross-lagged panel network estimates of centrality.

Note. Cross-Construct: In-prediction estimates for a given node at T2 by all nodes in the other construct at T1 (i.e., excludes any path connecting nodes from the same construct) and out-prediction estimates for a given node at T1 to all nodes in the other construct at T2. Larger values indicate greater centrality.