MAPPING THE COURSE OF AUD SYMTPOMS:

A NETWORK PERSPECTIVE

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a candidate for the degree of doctor of philosophy,

and hereby certify that, in their opinion, it is worthy of acceptance.

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DEDICATION

To Naomi, the Homies, and the Show Me.

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TABLE OF CONTENTS

LIST OF TABLES

Table

LIST OF FIGURES

Table

Page

ABSTRACT

Contemporary models of Alcohol Use Disorder (AUD) suggest a stage-like progression wherein certain features (i.e., symptoms) may play key roles in different stages of the disorder. For example, allostatic processes (tolerance, withdrawal) are suggested to play important role in escalation from recreational substance use to addiction, while cortico-striatal-limbic neuroadaptations have been found to contribute to craving and subsequent relapses. To further elucidate the role that individual symptoms of AUD play in the development and continuation of other symptoms, the current study used data from NESARC Waves 1 and 2 (n = 34,653) to explore how each individual symptom contributes to the onset, persistence, and recurrence of each other symptom of AUD. After creating subsamples for symptom onset, persistence, and recurrence, cross-lagged panel network models were calculated using Wave 1 symptoms to predict the presence of Wave 2 symptoms. The structure of the onset, persistence, and recurrence networks had low agreement, indicating that inter-symptom relationships differed as a function of course. High frequency, low severity symptoms had the greatest effect on the course of other symptoms, while the course of low frequency, high severity symptoms were most greatly influenced by other symptoms. While broad patterns emerged regarding symptom centrality, some symptoms appeared to have uniquely important roles in the various stages of course. When findings were compared to conceptual addiction models, results were mixed, and processes from multiple theoretical models were reflected in the data. Notable limitations include the presence of only two waves of data, issues related to symptom measurement and variable selection, and analytic limitations. The findings highlight need for additional work understanding the temporal course of individual AUD symptoms.

Chapter 1: Introduction

In both research and clinical practice, conceptualization of Alcohol Use Disorder (AUD) has been heavily influenced by the approach outlined in diagnostic manuals such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) and the International Classification of Diseases (ICD-11; World Health Organization, 2022). The prevailing diagnostic framework uses a symptom count approach which assumes that symptoms are polythetic (no one symptom is necessary or sufficient for diagnosis) and interchangeable (individual symptoms possess no functional significance beyond being [roughly] equivalent indicators for an underlying disorder). This approach has resulted in remarkable diagnostic heterogeneity (Lane & Sher, 2015), questionable diagnostic validity (e.g., Martin et al., 2011), and a lack of clear targets for assessment and intervention. Furthermore, the approach is disconnected from current theories on AUD, which emphasize the functional significance of different endogenous processes (indexed by symptoms) that result in addiction (e.g., Koob & Le Moal, 2001; Piazza & Deroche-Gamonet, 2013; Robinson & Berridge, 1993).

The National Institute on Alcohol Abuse and Alcoholism (NIAAA, 2019) describes AUD as a “chronic, relapsing brain disease.” Addiction, more broadly, has been characterized as a “progressive” disorder (American Society of Addiction Medicine, 2011; Piazza & Deroche-Gamonet, 2013). These definitions suggest that addiction is dynamic, evolving over time and featuring episodes of remission and recurrence. Further, contemporary models of addiction describe a staged, developmental process in which symptoms are functionally significant and have direct influence on other features/symptoms of the disorder. For example, allostasis (Koob & LeMoal, 2001) hypothesizes a cyclical model which illustrates how individual symptoms of addiction map on to each stage of the allostatic process. Opponent processes (contributing to *Tolerance*) result in a tonic change of the brain-body system, creating an allostatic state with altered hedonic set-points (resulting in *Withdrawal*), ultimately inducing changes in reward pathways that lead to impaired control over substance use (using *Larger Amounts over Longer Periods of time*, *Failed Attempts to Quit/Cut Down*). Incentive sensitization highlights how hypersensitization of the mesolimbic system results in craving and ultimately loss of control, implying that such symptoms are core features of addiction (Robinson & Berridge, 1993; 2008). The multistep theory (Piazza & Deroche-Gamonet, 2013) proposes three distinct stages of addiction, each with different features, culminating in loss of control over drug intake. Although these and other models differ in some key ways, they suggest that symptoms of addiction are meaningful beyond simple indication of a disorder. Furthermore, it is implied that not all symptoms used in diagnostic manuals (e.g., DSM, ICD) are equivalent indicators, with only some of the current diagnostic criteria capturing central features of addiction. Given these issues, there is a clear need for research on the relationship between individual symptoms and the process of addiction.

Symptom-Focused Approaches

Consistent with the notion of a latent "disorder" manifesting in a constellation of symptoms, research has historically focused on the syndrome, treating symptoms merely as indicators of this underlying construct or latent variable. In recent years, researchers have begun to consider alternative perspectives. The Cambridge Model (Marková, &

Berrios, 2009) highlights that symptoms per se have received little empirical attention, despite the crucial epistemological role that symptoms play in the field's understanding of psychological disorders. This model suggests that symptoms are complex phenomenon shaped by a variety of factors, and psychiatric research should focus on understanding symptoms themselves (Marková, & Berrios, 2009). Another approach, symptom network modeling, treats psychological symptoms not as indicators of an underlying disorder, but as an interconnected web of causally related problems that form into a mutually reinforcing network and that these symptoms *are* themselves the disorder (Borsboom & Cramer, 2013). While this approach has received methodological criticism (e.g., Forbes et al., 2019; Steinley et al., 2017; Neal et al., 2022), the surge in studies utilizing symptom network modeling (e.g., Contreras et al., 2019; Robinaugh et al., 2019) and rising interest in symptom focused approaches (e.g., Wilshire et al., 2021) indicate the field may be turning towards symptoms to solve the limitations of traditional psychological diagnostic systems.

Symptom Course

One important aspect of symptom network models is the notion of "activation." In the theorized causal process underlying the symptom network theory, a symptom can "activate" other symptoms within its cluster (i.e., other conceptually or empirically related symptoms), which can then go on to activate other symptoms or sustain the activation of other highly interconnected symptoms (Van Borkulo et al., 2016). Embedded within this theoretical framework lie notions about the course of the symptoms in question. For a symptom to be "activated," it is necessarily implied that this symptom was not previously manifest and is either a new onset or a recurrence of a previously (but not currently) experienced symptom. In the case of sustained activation, the relationship would be one of persistence, with the given symptoms each influencing the others to remain present.

Despite these meaningful temporal processes underpinning network theory, there is a dearth of symptom network research attempting to empirically isolate these aspects of course. Given the importance that the temporal processes of onset and maintenance play in the theoretical framework of symptom network models, there is a need for research attempting to explore how psychological symptoms influence not just the *presence* of other symptoms, but the *course* of other symptoms.

Symptom-Focused AUD Research

As symptoms appear to play an important role in theoretical models of addiction, there have been an increasing number of studies applying symptom network models to AUD. Huth and colleagues (2022) found loss of control (operationalized with *Larger/Longer* and *Cut Down*) to be the most central in a clinical sample network. This finding of Loss of Control's centrality is consistent with several other studies, (Conlin et al., 2022, Hoffman et al., 2019; Rhemtulla et al., 2016), and with theoretical arguments suggesting that "compulsion is a cardinal symptom of drug addiction" (Lüscher et al., 2020, p. 1). While this finding has achieved some replicability, AUD network structure has been found to vary between clinical vs. population samples (Hoffman et al., 2019; Huth et al., 2022), at different levels of life stress (Lin et al., 2020), when using different symptom cutoffs (Hoffman et al., 2018), and when comparing cross-sectional vs. cross-lagged panel networks (CLPN; Conlin et al., 2022).

While the body of network literature on AUD is growing, research on the course of individual AUD symptoms remains sparse. O'Neill & Sher (2000) found that *Tolerance* and *Withdrawal* had moderate persistence after one year and provided prognostic information about later AUD. Symptom course was found to differ by age, with some symptoms being less persistent and less predictive of AUD course in older adults (Vergés et al., 2021). Other covariates, including family history of AUD, personality, and heavy drinking were found to significantly predict the course of AUD, with predictors more nomologically proximal to AUD (heavy drinking, externalizing) having stronger effects than more distal predictors (family history of AUD, internalizing; Conlin et al., 2023). A recent study on AUD symptoms also found that more severe AUD criteria (e.g., withdrawal) are associated negative outcomes and comorbidities. Further, these high-risk criteria were also associated with an accelerated progression to severe AUD, relative to individuals who did not endorse these severe symptoms (Miller et al., 2023). This study highlights the heterogeneity among AUD criteria and the importance of studying temporal processes associated with individual symptoms. To the authors' knowledge, there are no previous studies that have attempted to use symptom network modeling while controlling for the temporal stage of the symptoms (onset, persistence, recurrence) to explore how AUD symptoms affect the course of other symptoms.

Current Study

The current study aims to bridge this gap in the literature by examining symptom course using an adapted CLPN approach to determine how each symptom impacts the onset, maintenance and recurrence of other symptoms. This approach extends beyond simply measuring the presence or absence of symptoms, which has important implications for the interpretation of the relationship between symptoms. In a traditional CLPN, the correlation between symptoms across time-points provides little information about the temporal "stage" of the symptom in question. While it provides evidence of some relationship, it does not indicate if the effect is an activation of a new symptom, the perpetuation of an existing symptom, or the recurrence of a previously deactivated symptom. Models lacking this information are still informative, however, the distinction between these various stages is an important part of the conceptual theory underlying the symptom network approach and how it relates to symptom course. As such, the current study aims to model the symptom networks so as to provide direct information about how different AUD symptoms predict the activation of new symptoms (onset), the continuance of existing symptoms (persistence), and the reactivation of once activated but presently dormant symptoms (recurrence).

Although symptom network modeling is inherently an exploratory approach, models of progression in preclinical literature enable the formulation of some working hypotheses regarding the relationships between symptoms. The allostasis theory suggests that opponent processes (contributing to *Tolerance*) create an allostatic state with altered hedonic set-points (resulting in *Withdrawal*), and lead over time to loss of control over alcohol use (Koob & Le Moal, 2001). Based on this theoretical model, we expected directional onset relationships with *Tolerance* predicting *Withdrawal* and *Withdrawal* predicting loss of control (failed attempts to *Cut Down* and drinking *Larger/Longer* than intended*)*. As this cycle becomes self-perpetuating, we expected loss of control symptoms to predict the persistence of *Tolerance*. Premised on incentive sensitization (Robinson & Berridge, 1993), we expected that *Withdrawal* (later stage of addiction represented by neurophysiological changes) would be a less robust predictor of symptom onset but would strongly predict other symptoms in the persistence and recurrence networks. While *Craving* would also be central to this hypothesis, the current study did not have access to measurements of this symptom at both waves of data. The "hijacking of the reward system" emphasizes compulsion as a critical feature of addiction (e.g., Volkow et al., 2003). Based on this model, we expected *Give Up* important activities to continue drinking, drinking despite *Physical/Psychological* problems, excessive *Time Spent* on alcohol (indicating preoccupation), and *Role Interference* to be central symptoms. As compulsion is thought to be a late-stage manifestation, we expected these symptoms to be strongly predicted by other symptoms in the onset and recurrence models and be a strong predictor of other symptoms in persistence models. However, as rapid reinstatement models of addiction (e.g., Bossert et al., 2013) indicate that compulsive drug use is quickly reinstated even after a period of abstinence, compulsive symptoms were also posited to be strong predictors in recurrence models.

The multistep theory (Piazza & Deroche-Gamonet, 2013) acts as an overarching theory that incorporates other conceptual models of addiction in a stage-like process: recreational substance use, followed by neurobiological changes resulting in intensified drug use, ultimately leading to loss of control and full addiction characterized by compulsive substance use. In line with this theory, we expected the onset and recurrence models to find *Hazardous Use* (our closest proxy to sporadic/recreational use) predicting onset of *Tolerance* and *Withdrawal* (proxies for neurobiological changes associated with worsening addiction), and *Tolerance* and *Withdrawal* predicting the onset of *Cut Down*, *Larger/Longer*, and drinking despite *Physical/Psychological* problems (proxies for loss of control and compulsivity). In the persistence model, assuming the presence of addiction, we expected loss of control (*Cut Down*, *Larger/Longer*) to most greatly influence the maintenance of other symptoms.

Chapter 2: Method

Sample

The proposed study used data from the two waves of the National Epidemiological Study on Alcohol and Related Conditions (NESARC). NESARC is a nationally representative sample collected by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in 2001-2002 (Grant, Moore, et al., 2003) and again in 2004-2005 (Grant et al., 2005). NESARC (N=43,093; 52% female; mean age=46.4, SD=18.1) was composed of a representative sample of the US noninstitutionalized civilian population, 18 years or older at baseline, examining alcohol and drug use, psychiatric disorders, risk factors, and consequences. A complex sampling structure was used to obtain a nationally representative sample. Three years later, 86.7% of these participants completed a follow-up survey at Wave 2 (N=34,653; 53% female; mean age=49.1, SD=17.3). The racial demographic of the sample was 58.2% White, 19.0% Black, 1.6% Indigenous Americans, 2.8% Asian and Pacific Islander, and 18.4% non-white Hispanic. Interviews were conducted by experienced lay interviewers from the U.S. Census Bureau, who had received 10 days of training on administering survey instruments and collecting participant data. More detailed information about the sampling and interview process is documented by Grant and colleagues (2004).

Measures

The NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV; Grant et al., 2001) was used to measure the DSM-IV criteria for Alcohol Abuse and Alcohol Dependence, along with other substance use disorders. Craving is the only DSM-5 AUD symptom that is unavailable, with Craving only being measured at Wave 2. The symptoms were defined as follows: Tolerance = "Tolerance, as defined by either of the following: (a) A need for markedly increased amounts of alcohol to achieve intoxication or desired effect (b) A markedly diminished effect with continued use of the same amount of alcohol." Cut Down = "There is a persistent desire or unsuccessful efforts to cut down or control alcohol use;" Larger/Longer = "Alcohol is taken in larger amounts or over longer periods than was intended;" Time Spent = "A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects;" Give Up = "Important social, occupational, or recreational activities given up or reduced because of alcohol use;" Physical/Psychological = "Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol." Withdrawal = "Withdrawal, as manifested by either of the following: (a) The characteristic withdrawal syndrome for alcohol, (b) Alcohol (or a closely related substance, such as benzodiazepine) is taken to relieve or avoid withdrawal symptoms." Hazardous Use = "Recurrent alcohol use in situations in which it is physically hazardous." Social/Interpersonal = "Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol." Failure to Fulfill= "Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home."

The AUDADIS–IV is a structured diagnostic interview developed to measure psychiatric problems in large-scale data. Evidence supporting the reliability and validity of the measure is well documented (e.g., Grant, Dawson, et al., 2003; Hasin et al., 2003) and has been researched in clinical samples (Hasin, Carpenter, et al., 1997) and community samples (Hasin, Van Rossem, et al., 1997). The AUDADIS-IV used at Wave 2 included several new modules and risk factors, which were also found to be psychometrically valid and reliable (e.g., Ruan et al., 2008). Consistent with the DSM-IV, current diagnosis required the endorsement of a symptom during the past 12 months.

While there is evidence for the reliability and validity of the AUDADIS-IV, it should be noted that the psychometric properties of the Alcohol Abuse and Alcohol Dependence modules have been documented primarily at the sydromal or diagnostic level. Test-retest reliability estimates for combined Alcohol Abuse and Alcohol Dependence in a clinical sample found high agreement (Cohen's Kappa = 0.74), with Intraclass Correlation Coefficient estimates for Alcohol Abuse and Alcohol Dependence symptom count equal to 0.82 and 0.86, respectively (e.g., Hasin, Carpenter, et al., 1997). However, the current study was conducted on the level of individual criteria, which are consist of one or more items, and evidence of reliability at the diagnostic level does not necessarily indicate reliability at the item level.

Analytic Approach

The study used the method demonstrated by Conlin and colleagues (2022) to conduct cross-lagged panel networks (CLPN) in binary data. To generate

CLPN, binary auto-regressive analyses (Fahrmeir & Tutz, 1994, 2001) were conducted, with each symptom at Wave 2 regressed on all symptoms (including the Wave 1 measurement of the outcome symptom) at Wave 1. SAS procedure SURVEYLOGISTIC was used to account for the primary sampling unit, stratum, and sampling weights of the NESARC data using Wave 2 sampling weights. The unstandardized regression coefficient responding to each symptom was then used as the directed edge weight for the corresponding element in the adjacency matrix underlying the symptom network. This method has been used in several studies (Conlin et al., 2022; Funkhouser et al., 2021; Rubin et al., 2021), but is admittedly limited due to the inability to parse within- and between-subject effects without at least 3 waves (Hamaker & Grasman, 2014; Hamaker et al., 2015). The qgraph package was used for network visualization (Epskamp et al., 2012).

Course. As noted by Conlin and colleagues (2022), interpretation of whole-sample prospective SNMs is limited by the absence of information regarding the temporal stage of each symptom. When simply calculating the likelihood of a symptom predicting another symptom at a future timepoint, the results fail to differentiate between new instances of symptoms, continuation of already existing symptoms, or recurrence of previously remitted symptoms. To address this limitation, we examined inter-symptom relationships surrounding the onset, persistence, and recurrence of each symptom (in contrast to traditional CLPN models, where the symptom at Time 1 predicts a symptom at Time 2 unconditionally). The NESARC data was subset based on prior and current patterns of symptom endorsement (Table 1). Onset analyses included participants who did not have lifetime endorsement of the given symptom and did not endorse the symptom at Wave 1. Persistence analyses included participants who endorsed the symptom at Wave 1 (with or without lifetime endorsement). Recurrence analyses included participants who endorsed experiencing the symptom at some point in their lifetime prior to Wave 1, but did not endorse the symptom at Wave 1.

Course Networks. To generate networks of symptom course, the data was conditioned into subsamples. For each symptom (out of 10 symptoms), the data was divided into three non-overlapping subsamples based on the temporal stage of the given symptom (onset, persistence, recurrence), using the method described above and resulting in a total of 30 subsamples (stages of course [3] multiplied by number of symptoms [10]). A symptom network model was generated in each, for a total of 30 models. Each network displayed the relationship between each other symptom, based on the temporal stage (never endorsed, endorsed in the past 12 months, or endorsed prior to the last 12 months but not in the past 12 months) of the symptom which the network was conditioned on.

Aggregate Networks. Due to the large number of models and edges within these networks, an additional 3 aggregate networks were generated. These networks were constructed by extracting the node and edges from each course network that corresponded to the symptom that the network was conditioned on (e.g., in the three networks generated from *Tolerance* subsamples, the Tolerance node and edges were extracted). These edges were then combined together into a single network, enabling a visual representation of how each individual symptom influenced the course of each other symptom (e.g., in each subset of *Tolerance* at Wave 1 [onset, persistence, recurrence], how does each other symptom predict

Tolerance at Wave 2). While this "network" provides a useful summary of the edges that pertain directly to symptom course, it consists of various samples with some degrees of overlapping data and a wide range of sample sizes, and thus the interpretability of this aggregate network is limited.

Unconditioned network. Along with the networks conditioned on the course, an overall "unconditioned network" was generated. This network is a traditional CLPN of Wave 1 symptoms predicting Wave 2 symptoms, without attention to symptom course. This unconditioned CLPN has been explored and discussed in further detail elsewhere (Conlin et al., 2022), and the network is only used in this paper as a reference for comparing the agreement of the course networks (i.e., examining if the course networks each provide unique information, and determining if this information is not captured in the overall network).

Network Agreement

To determine if the various course networks provided unique information, network agreement across the forms of course was tested. As we hypothesized that inter-symptom relationships vary as a function of course, we expected consistency between the networks to be low. Network agreement was addressed in multiple ways. General agreement was calculated using a correlation of the edge weights across forms of course and with the edge weights of the Unconditioned network. Intraclass correlations (ICC; Shrout & Fleiss, 1979; Shrout & Lane, 2012) of networks were examined across course to determine the general agreement between the three course networks. Additionally, using a method utilized by Funkhouser and colleagues (2021), agreement between specific edges was examined by measuring the proportion of individual edges that directionally replicated in each network (e.g., specific edges were positive or negative across all networks). Network agreement was calculated separately across the 3 different forms of course (onset, persistence, recurrence), and calculated in combination with the Unconditioned network to determine the extent that various stages of course differed from the overall network structure. Pairwise comparisons were also conducted on the edges pertaining to symptom course (aggregate network edges) to explore if specific forms of course were driving the effect, with Cohen's Kappa being used to test agreement beyond chance (Cohen, 1968).

Centrality estimates (strength, closeness, betweenness; Opsahl et al., 2010) were also calculated for the three networks. As closeness and betweenness have received considerable criticism regarding their utility for symptom network models (e.g., Hallquist et al., 2021), strength was the main aspect of centrality used in interpretation of models. As there are two waves of data, results were discussed in terms of outstrength (the extent to which a symptom predicts other symptoms) and instrength (the extent to which a symptom is predicted *by* other symptoms). Finally, the results were then compared to the endogenous processes of theoretical models of addiction, as outlined in the hypotheses section.

Chapter 3: Results

Course Networks

Briefly discussed here are some of the key findings regarding the average strength of each network, while full summaries of mean edge weights by symptom subset and course can be found in Table 2. On average, the Recurrence networks had the greatest degree of connectivity (mean edge weight = 0.781). When averaging across forms of course, *Withdrawal* subsets had the greatest connectivity (mean edge weight = 0.777) but were closely followed by *Larger/Longer* and *Failure to Fulfill* (mean edge weights = 0.734 and 0.705, respectively). When accounting for the direction of the associations (positive or negative), Onset networks had the greatest overall connectivity (mean edge weight = 0.443). With this method, *Tolerance* had the greatest amount of overall connectivity (mean edge weight = 0.407), followed by *Cut Down* (mean edge weight = 0.384) and *Failure to Fulfill* (mean edge weight = 0.361). There were considerable differences in network structure between symptom subsets (e.g., between the networks subset on *Larger/Longer* and the networks subset on *Tolerance*), and between course networks within symptom subsets (e.g., between the *Larger/Longer* Onset network and *Larger/Longer* Persistence network). Broadly, there were considerable differences in network structure between symptom subsets (e.g., between the networks subset on *Larger/Longer* and the networks subset on *Tolerance*), and between course networks within symptom subsets (e.g., between the *Larger/Longer* Onset network and *Larger/Longer* Persistence network). Below we highlight specific findings from each stage of course, the results of the aggregate networks, and the degree of agreement between networks associated with different stages of course.

Onset Networks

Figure 1 and Figure 2 display the results of the Onset symptom network models. While predicted edges vary considerably, the edges that directly index prospective prediction from a target baseline symptom (i.e., those specifically pertaining to symptom course) are relatively consistent across models. Of edges related to symptom onset, the strongest edge was *Cut Down* predicting new onsets of *Social Interpersonal Problems* (edge weight = 1.26) and *Hazardous Use* predicting new onsets of *Larger/Longer* (edge weight = 1.11). While these were the strongest edges, there were many edges with similar (albeit slightly weaker) relationships. Centrality estimates of each node in its pertaining course network (plotted in Figure 3) indicate that, while there is some variability, each symptom has a surprisingly stable pattern of prediction on the course of each other symptom. *Cut Down* and *Hazardous Use* have the lowest average instrength (3.5 and 3.1, respectively), indicating that other symptoms have relatively little influence on new onsets of these symptoms. *Failure to Fulfill* had the highest average instrength (5.7), with new onsets of this symptom most highly predicted by other symptoms. *Withdrawal* and *Larger/Longer* were the symptoms with highest average outstrength, indicating that these symptoms were the most likely to predict onsets of new symptoms. The patterns of strength centrality found in *Hazardous Use* and *Larger/Longer* onset less closely resembled the trends found in the other 8 symptoms, suggesting that these symptoms may have a unique role in the context of new symptom development.

Persistence Networks

Figures 4 and 5 display the results of the Persistence symptom networks. Like the Onset networks, there is a variability in the symptom networks between symptom subsets. Potentially due to the comparatively small sample sizes, some of the edges associated with low base rate/high severity symptoms produced larger and less stable estimates. However, the edges corresponding to the course of the symptom (directional edges pointing towards the symptom on which the data is subset) are generally stable across all symptom subsets. Of edges pertaining to symptom persistence, the strongest relationship was *Withdrawal* predicting the persistence of *Failure to Fulfill* (edge weight = 2.59). To a lesser degree than the Onset networks, the centrality measures of symptom persistence displayed a somewhat consistent pattern across symptom subsets (Figure 6). The *Give Up* and *Failure to Fulfill* subsets did not wholly adhere to these trends, with all symptoms having high levels of strength and closeness in these subsets. *Failure to Fulfill* and *Give Up* had the greatest average instrength across subsets (means = 4.6 and 4.7, respectively), while *Social/Interpersonal Problems* and *Withdrawal* had the highest average outstrength (means = 4.8 and 5.3, respectively).

Recurrence Networks

Figures 7 and 8 display the results of the Recurrence symptom networks. The Recurrence networks varied considerably between each symptom subset. Most notably, the Recurrence networks display a considerable number of strong negative edge, with the majority connected to nodes associated with lowest frequency symptoms (*Failure to Fulfill*, *Give Up*). However, many of these edges are not connected to the symptom on which the data was subset and do not provide information about symptom course (e.g., the relationship between *Give Up* and *Time Spent* when sub-setting for recurrence of *Failure to Fulfill)*. Of edges pertaining to symptom recurrence, the strongest edges were *Time Spent* predicting the recurrence *Failure to Fulfill* (edge weight = -4.74) and *Give Up* predicting recurrence of *Failure to Fulfill* (edge weight =3.41). While a pattern emerged in symptom centrality (Figure 9), this pattern was less pronounced than in the Onset and

Persistence networks. The *Withdrawal* subset had especially idiosyncratic patterns, with very high strength centrality estimates for several symptoms. As in the Persistence networks, *Give Up* and *Failure to Fulfill* had the greatest average instrength (means = 9.0 and 10.4, respectively), but there was considerably more variability between symptom subsets than in other forms of course. There was no single symptom that appeared to have an especially strong outstrength, and outstrength estimates varied widely between symptom subsets.

Aggregate Networks

As noted, due to the network edges being drawn from multiple subsamples, the interpretability of the aggregate networks (Figure 10) using the traditional network theory approach may be limited. However, as the edge weights are equal to the edge weights produced in the full network, these networks provide a useful summary of the relationships in the course networks that directly pertain to the course of individual symptoms. Likewise, the strength centrality estimates (Figure 11) of these edges provide a useful summary of the overall influence symptoms have on the course of other symptoms. While there were differences between the three forms of course, some patterns in symptom instrength and outstrength did emerge. *Failure to Fulfill* had the greatest average instrength across forms of course (mean = 8) indicating that the course of this symptom may be especially prone to influence from other AUD symptoms. No single symptom had the uniquely high average outstrength across forms of course, with *Give Up* (mean = 5.33), *Social/Interpersonal Problems* (mean = 5.37), and *Larger/Longer* (mean = 5.6) having similar average outstrength.

Network Agreement

Overall correlation of edge weights can be found in Table 3. Across all subsamples and in the aggregate network, Onset and Persistence networks were significantly correlated (range = 0.20 - 0.46, $p < .05$). Onset and Recurrence networks were also significantly correlated in all subsamples, with greater overall agreement (range = 0.21 - 0.83, $p < .05$). Less agreement was observed between the Persistence and Recurrence networks, with 5 subsamples having significant positively correlated edges (range = 0.20 - 0.46, $p < .05$), four subsamples having non-significant correlations (range = -0.02 - 0.16, $p > .05$), and the *Withdrawal* subsample having significant negative correlation ($r = -0.20$, $p < .05$). The Onset and Recurrence aggregate networks were not significantly correlated ($r = .08$). Edge weight correlations were also examined between each course network and the Unconditioned network (see Figure 3). Except for the Recurrence and Unconditioned network ($r = .06$), each of the course networks were significantly correlated with the Unconditioned network (range = 0.20 - 0.89, $p > .05$). The Onset network and Persistence networks were generally moderate-strongly correlated with the Unconditioned network, while the Recurrence network had a weaker association. In the aggregate networks, only the Onset network was significantly correlated with the Unconditioned network ($r = 0.17$, $p < .05$). As expected due to similarities in network structure, agreement in symptom centrality followed similar patterns between each form of course. Symptom centrality agreement was generally high between Onset and Persistence networks, with lower agreement between Onset and

Recurrence networks, and more modest agreement between Persistence and Recurrence networks.

Intraclass correlation was calculated to determine the overall network agreement in each subsample. Course network reliability ranged from very low in the *Withdrawal* subsample (ICC = .02) to moderate in the *Cut Down* subsample (ICC = .51). Agreement between the aggregate networks was poor (ICC = 0.21). Variance compositions of the networks indicated that the pattern of edge weights (e.g., does the value of a given edge differ across forms of course) varied between forms of courses (see Table 3). As the aggregate network edges consist of only those that capture the course of each symptom and are thus the most relevant to the research question, the weights of these edges have been plotted in Figures 12-15. These plots have been divided into the conceptual criteria groups outlined in the DSM-5 (American Psychiatric Association, 2013). Stage of course appears to make little difference in how other symptoms influence the course of Pharmacological criteria (*Tolerance, Withdrawal*; Figure 15), while stage of course was considerably altered the inter-symptom relationships on Social Impairment criteria (*Social/Interpersonal Problems, Failure to Fulfill, Give Up;* Figure 13).

The proportion of edges that agreed across all three forms of course (see Table 4) ranged from 0.67 in the *Tolerance* subset to 0.42 in the *Give Up* subset. When also including agreement with the Unconditioned network, the range was unchanged (0.67 in *Tolerance* to 0.42 in *Give Up*). Indeed, there were very few instances in which edges agreed across the 3 forms of course but did not agree with the Unconditioned network. There was considerable variability in which edges were most stable across the subsets, with several edges (e.g., *Larger/Longer* predicting *Hazardous Use*) agreeing across course in 100% of the subsets, while there were also some edges (e.g., *Hazardous Use* predicting *Tolerance*) that agreed across course in 0% of the subsets. Averaging across symptom subsets, the proportion of edges that replicated in all forms of course was 0.54).

Edge replication analyses were also conducted on the edges specifically pertaining to symptom course (aggregate network edges), with 56% of edges replicating across all 3 networks, and 44% replicating across the three course networks and the Unconditioned network. Additional analyses were conducted on pairwise combinations to further explore differences in agreement by course (Table 4). The proportion of edges that replicated in two course networks ranged from 0.81 in the Onset and Recurrence networks, to 0.64 replicating between the Persistence and Unconditioned networks. As a disproportionate number of edges were positive in all of the networks, Cohen's Kappa (Cohen, 1968) was calculated to determine the extent to which networks agreed beyond chance. Moderate agreement was found between the Onset and Recurrence edges (k = 0.54), slight systematic disagreement was found between the Persistence and Unconditioned networks (k = -0.15), and low agreement (k range = 0.15 – 0.21) was found between the remaining pairwise comparisons

Hypothesized Relationships

There was inconclusive evidence to support the hypothesized relationships of specific symptoms based on their function in theoretical models. On the hypothesis related to allostasis, *Tolerance* was among the weaker predictors of new onsets of

*Withdrawal (*edge weight = 0.20). However, *Withdrawal* was a stronger predictor of new Onsets of loss of control symptoms, being among the strongest predictors of *Larger/Longer* (edge weight = 0.92), *Cut Down* (edge weight = 0.66), and *Time Spent* (edge weight = 0.77). In the hypothesis related to incentive sensitization (which is admittedly limited due to the lack of *Craving* measurement), we found little evidence that *Withdrawal* would more strongly predict symptom persistence and recurrence. Contrary to this hypothesis, *Withdrawal* was a stronger predictor of symptom onset (mean edge weight = 0.64) than symptom persistence (mean edge weight = 0.43) or symptom recurrence (mean edge weight = 0.40).

There was mixed evidence for the hypothesis related to "hijacking of reward system," which hypothesized high instrength for symptoms related to compulsion in the Onset and Recurrence networks, and high outstrength for these symptoms in the Persistence networks. *Give Up* had high instrength in the Persistence (mean instrength = 4.7) and Recurrence models (mean instrength = 9.0), with moderate centrality in the Onset networks (mean instrength = 5.1). *Give Up* outstrength was only large in the Recurrence networks (average outstrength = 10.1). *Failure to Fulfill* had high instrength in the Onset (average instrength = 5.7), Persistence (mean instrength = 4.6), and Recurrence (mean instrength = 10.4) networks, but only had high outstrength (mean outstrength = 7.8) in the Recurrence networks. *Physical/Psychological* had moderate instrength in the Onset models (mean instrength =4.5) but had low strength centrality in the Recurrence and Persistence models. *Time Spent* had moderate instrength in the Onset (mean instrength = 4.8) and Recurrence networks (mean instrength = 6.1), but low instrength in the Persistence networks and low average outstrengh in all forms of course.

In relation to the multistep theory, *Hazardous Use* was the strongest predictor of *Withdrawal* (edge weight = 0.88) but was a relatively weak predictor of *Tolerance* (edge weight = 0.18). As noted above, *Withdrawal* was a strong predictor of new onsets of loss of control symptoms (*Cut Down*, *Larger/Longer*, *Physical/Psychological*), but *Tolerance* did not have uniquely strong effects on these symptoms. There was also a lack of evidence for the hypothesis that loss of control symptoms would be the strongest predictors of symptom persistence.

These results provide insight into specific symptom relationships, the extent to which they alter as a function of course, and an insight into broad similarities and differences in inter-symptom relationships during different stages of symptom course. The results also indicate that stage of course changes the associations among symptom and that each (onset, persistence, and recurrence) is different from the others and from the structure found in an overall (not adjusted for symptom course) CLPN. Regarding our hypothesis about specific symptom relationships based on theoretical models, the findings offered support for some of the hypothesized relationships and lack of support for others. However, none of the findings related to any of the theoretical models offered conclusive evidence in support of any of the proposed hypotheses.

Chapter 4: Discussion

This study used CLPN to determine the extent to which inter-symptom relationships varied as a function of the stage of course of each symptom, Additionally, the observed relationships between symptoms were compared to the theoretical relationships posited by various conceptual models of addiction. The use of data sub-setting based on each symptom allowed the longitudinal symptom networks to model edges denoting the effect that each symptom had on the onset, persistence, and recurrence of each other symptom.

Within each model, nodes were highly interconnected and featured a mixture of both positive and negative edges, with the proportion of negative edges increasing smaller subsamples and in edges involving low frequency symptoms. Agreement across the different forms of networks was generally low, indicating that new information is gained when controlling for the stage of course of a given symptom. While the study did not find evidence for specific course-bound processes posited in theoretical models, the results help to create a deeper understanding of the relationship between AUD symptoms over time. The interpretation of these relationships is described below, but it should be noted that due to the presence of only 2 waves of data, the study was unable to model random intercepts and cannot isolate between- and within-subject effects. As such, there is a limited ability to determine the extent to which these findings are representative of intra-individual processes of symptom progression.

Onset networks most closely resembled hypothesized relationships and had the greatest average relationships when accounting for positive and negative edges. Regarding symptom onset, the strongest effect was *Cut Down* predicting new onsets of *Social/Interpersonal Problems,* suggesting that social dysfunction may be most likely to arise (relative to other symptoms) following failed attempts to curtail drinking. For symptom onset, *Larger/Longer* and *Hazardous Use* were the most central symptoms. While this may have specific implications regarding the conceptual importance of these symptoms, based on previous findings related to symptom course (Conlin et al., 2023), we believe this finding may largely be due to symptom base rate and severity. Specifically, *Larger/Longer* and *Hazardous Use* have high base rate frequency and are less indicative of severe AUD (Boness et al., 2019). Regarding high outstrength, these symptoms may be more likely to appear early in the disorder, and predict the subsequent onset of new, more severe, symptoms. Regarding high instrength, an individual experiencing high threshold symptoms (indicative of more severe AUD) may be expected to also begin exhibiting the lower threshold symptoms.

Persistence networks had weaker inter-symptom relationships than the Onset and Recurrence networks and had a higher proportion of negative edges than the Onset networks, but a lower proportion than the Recurrence networks. Edge weights and proportion of negative edges generally increased as sample sizes decreased. There may be several reasons for these negative edges. First, the smaller sample sizes may result in less reliable estimates. Second, the presence of less severe symptoms may indicate that the disorder is remitting or decreasing in severity. Third, due to the low base rate of these symptoms, the likelihood that these symptoms are not endorsed again at Wave 2 is increased, simply due to random chance (i.e., if a symptom has a very low probability of being endorsed at Wave 1, regardless of the presence of other symptoms, the probability of it being endorsed at Wave 2 is relatively low compared to other high-frequency symptoms). The strongest relationship in the Persistence networks was *Withdrawal* predicting the persistence of *Failure to Fulfill,* indicating that if an individual is having difficulty fulfilling their responsibilities, and is experiencing physiological withdrawal symptoms, they are likely to continue having difficulty fulfilling their obligations. *Failure to Fulfill* and *Give Up* had the highest average instrength, indicating that chronicity of symptoms related to role impairment are especially sensitive to the presence of other symptoms. *Social/Interpersonal Problems* had the highest average outstrength, suggesting that impaired social functioning is a strong risk factor for persistence of other AUD symptoms.

Recurrence networks had fewer positive relationships than Onset and Persistence but had the greatest absolute edge strength. As with persistence, the proportion and strength of negative edges increased as sample size decreased and were generally found connecting to the lowest frequency/highest severity nodes (*Give Up, Failure to Fulfill)*. This is likely due to similar reasons as described in the Persistence network, but with additional error due to reliance on lifetime symptom reporting. The strongest positive edge related to symptom recurrence was *Give Up* predicting the recurrence of *Failure to Fulfill*. This relationship is unsurprising, as the presence of a severe role impairment symptom would logically predict the recurrence of another. However, the inverse relationship is negative, indicating the *Failure to Fulfill* actually decreases the likelihood of experiencing a recurrence of *Give Up*. Idiosyncratic findings such as these indicate that further research will be required to understand symptom recurrence, and the combination of small subsamples, low base rate, and lifetime symptom reporting may seriously limit the interpretability of these effects.

Comparisons of the agreement across different course networks suggest that the stage of course is an important factor to consider when examining symptom networks. The various methods of agreement each found that there is some degree of consistency in inter-symptom relationships across the different forms of course, but there is also a considerable amount of difference. Reliability ranged from low to moderate and global correlations of edge weights ranged from low to high. Only approximately half of edges directionally replicated across the three networks, and when accounting for chance, the proportion of edge replications was poor. Agreement between Onset and Recurrence was greatest, which may be due to both involving the Wave 2 acquisition of a symptom that was not endorsed at Wave 1. Agreement between Persistence and Recurrence was especially poor, with half of the subsamples having low, insignificant, or negative correlations between these forms of course. This may be due to a combination of different inter-symptom processes involved in the continued AUD or relapse, and due to lower subsample sizes in these networks. While the course networks differed from one another, they all also differed from the Unconditioned network, further indicating that stage of symptom course provides unique information not captured by traditional CLPN.

Limitations and Future Directions

The most notable limitations of this study can broadly be categorized as (a) measurement limitations and (b) analytic limitations. In measurement limitations, there are several issues worthy of discussion. There are only two time-points of measurement, which generally limits the ability to follow trends or capture any changes that occur in directionality or magnitude over time. Further, there is no reason to expect that a three-year interval is the ideal window of time to measure these inter-symptom relationships, and it is fully possible (if not likely) that there are changes in the progression of AUD symptomatology that need shorter or longer periods of measurement to be properly observed. Related to time-bound processes, the study is also limited in its ability to measure symptom course. With only two waves of data, and "present" symptom relationships being defined as "during the past 12 months," there is a fair amount of error that likely arises from these crude definitions of course. For example, "Persistence" relies on an individual endorsing a symptom at Wave 1 and again at Wave 2, but this does not guarantee that the symptom continually persisted during three years between measurement. Measurement of recurrence is especially limited, as the category relies on lifetime reporting. The accuracy of retrospective lifetime symptom measurement has been questioned for AUD measurement (Haeny et al., 2016) and for psychiatric symptomatology more broadly (Moffitt et al., 2010; Vandiver & Sher, 1991).

The study has several limitations related to the measurement of symptoms. Issues relating to crude measurement and dichotomous categorization of AUD symptoms has been discussed in the literature (e.g., Helzer et al., 2006; Watts et al., 2021). As these issues relate to this study, dichotomous symptoms provide a limited ability to track the course of a given symptom, and this is exacerbated by the presence of only two measurement points. Future research on symptom course may benefit from dimensional measurement of symptoms and additional waves of data. The crude measurement also presents challenges for symptom networks, as the symptoms are central to the theoretical model. While the study uses diagnostic criteria, the current diagnostic scheme of one symptom per criterion may not be the best method for this approach. There may be additional symptoms or processes that should be included in the network to avoid model misspecification due to variable omission, or there may be redundant/unnecessary nodes that should not be included in the network. Lastly, previous work has shown that different operationalizations of a criterion have different thresholds for endorsement (Boness et al., 2019; Lane et al., 2016; Hoffman et al., 2018), resulting in considerable changes to the base rate and severity of a given symptom. Future work should attempt to explore how different operationalizations impact the structure of the network. In addition to symptom network modes, future research on symptom course may also make use of methods such as latent transition analysis to identify classes of symptoms profiles and examine how individuals transition among these classes.

The current study also has notable analytical limitations. As previously noted, random intercepts cannot be modeled due to the presence of only two waves of data. As such, we were unable to fully parse between- and within-subject effects, limiting the extent to which these results can be interpreted as intra-individual changes in symptomatology. Future research on using three or more waves of data is needed to determine the extent to which these findings are applicable to individual within-person symptom relationships. Additionally, while the initial sample is large, the sub-setting required to control for course on low prevalence symptoms drastically reduces some sample sizes. In these reduced samples, the number of individuals endorsing other rare symptoms can become very low, and this is reflected by the relatively unstable and difficult-to-interpret relationships found in some of the networks. Additional research on a clinical sample with more consistent base rates of symptoms may help to ameliorate this limitation. Further, the available tools for comparing and analyzing CLPN are limited, relative to the available software for cross-sectional and intensive longitudinal networks. Future advancements in software for CLPNs will allow for more sophisticated analyzation of these relationships.

Finally, a limitation of this study, and perhaps the network approach more broadly, is uncertainty about the underlying properties of the nodes that constitute the symptom network. While a full discussion of this limitation is beyond the scope of this paper and has been discussed in greater detail elsewhere (e.g., Guloksuz et al., 2017; Hallquist et al., 2021). Most relevant to this study, a key component of this limitation is the lack of item-level psychometric data. In these symptom network models, each node consists of a single criterion measured by the endorsement of one or more items related to the given symptom. However, there is a dearth of research indicating the validity or reliability of these individual items. Rather, there is extant evidence that these items (that are presumed to be interchangeable) have different thresholds for endorsement and can alter symptom network structure depending on which of the items is endorsed for measuring the given symptom (Hoffman et al., 2018). Alternatively, it is possible that there are items which have virtually no discriminative value beyond the other items measuring the symptom and are simply introducing “noise” into the network. Future research should use Item Response Theory (IRT) or other techniques to determine the extent to which the items constituting each node or symptom are reliable and valid measurements of the given symptom.

Conclusion

With the increasing attention being paid to individual symptoms and their relationships, the current study highlights additional factors that should be considered in this line of research. Although a lack of evidence was found in support of hypothesized relationships related to specific theoretical models, the study found that the influence that a given symptom has on other symptoms differs as a function of symptom course. In some symptoms, the differences are simply the strength of the relationship, while other symptoms have changes in both strength and directionality. While specific inter-symptom relationships vary, clear trends in symptom centrality emerge, indicating that certain symptoms may have more or less impact on the other symptoms, regardless of whether a given symptom is already present. Future work focused on better understanding the onset, persistence, and recurrence of symptoms may have important implications for understanding the development of AUD and assist in prevention. Further, studies approaching the treatment of AUD and symptom desistance from a network perspective may provide vital information for intervention and recovery from addictive disorders. While additional research is needed to replicate the specific findings and improve our understanding of the effects of course on symptom networks, this study provides strong initial evidence that the temporal stage of symptoms should be considered in future research in this field.

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Table 1.
Symptom Course as Defined by Endorsement Patterns

	Prior to Wave 1	Wave 1	Wave 2
Persistence	LT[a]	PY	PY
Onset	-	-	PY
Recurrence	LT	-	PY

Note. "LT" Represents the lifetime presence of the symptom, "PY" represents the presence of a symptom in the past year prior to the given timepoint. "-" represents the absence of a symptom at a given time.
[a]For persistence, lifetime endorsement prior to past year was allowed but not sufficient while PY at Wave 1 was necessary and sufficient.

Table 2.
Average Edge Weights

Absolute Value

	Onset	Persistence	Recurrence	**Total**	Average
LL	0.734	0.345	1.138	**2.218**	0.739
CD	0.614	0.362	0.597	**1.573**	0.524
HU	0.691	0.367	0.743	**1.801**	0.600
WD	0.625	0.338	1.369	**2.332**	0.777
TL	0.553	0.391	0.468	**1.412**	0.471
PP	0.547	0.393	0.773	**1.713**	0.571
TS	0.588	0.421	0.578	**1.586**	0.529
SI	0.532	0.378	0.536	**1.445**	0.482
FF	0.535	0.790	0.792	**2.116**	0.705
GU	0.521	0.499	0.814	**1.834**	0.611
Total	**5.939**	**4.285**	**7.807**	**18.031**	
Average	0.594	0.428	0.781		

Positive/Negative Values

	Onset	Persistence	Recurrence	**Total**	Average
LL	0.448	0.285	0.010	**0.295**	0.098
CD	0.486	0.261	0.404	**1.151**	0.384
HU	0.360	0.303	0.302	**0.965**	0.322
WD	0.384	0.268	-0.357	**0.295**	0.098
TL	0.514	0.263	0.443	**1.220**	0.407
PP	0.494	0.246	0.107	**0.847**	0.282
TS	0.440	0.259	0.324	**1.023**	0.341
SI	0.436	0.222	0.277	**0.935**	0.312
FF	0.437	0.408	0.237	**1.082**	0.361
GU	0.429	0.200	0.239	**0.868**	0.289
Total	**4.428**	**2.715**	**1.986**	**9.129**	
Average	0.443	0.272	0.199		

Note. Values listed are the mean of the edge weights associated with a given node (symptom) across all 10 symptom subsets in each form of course. Absolute weights indicate the overall strength of influence a given symptom has on other symptoms. Positive/negative allows for negative values in the mean calculation, providing a clearer sense of which symptoms increase the likelihood of other symptoms. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Table 3.
Edge Weight Correlation by Course Network

		Pearson Correlation				
		Onset	**Persistence**	**Recurrence**	**Unconditioned**	**ICC**
Aggregate	Onset	1	-	-	0.17*	0.21
	Persistence	0.20*	1	-	-0.1	
	Recurrence	0.50*	0.08	1	0.12	
Larger Longer	Onset	1	-	-	0.62*	0.17
	Persistence	0.39*	1	-	0.78*	
	Recurrence	0.45*	0.24*	1	0.37*	
Cut Down	Onset	1	-	-	0.70*	0.51
	Persistence	0.50*	1	-	0.74*	
	Recurrence	0.72*	0.47*	1	0.55*	
Hazardous Use	Onset	1	-	-	0.66*	0.49
	Persistence	0.29*	1	-	0.70*	
	Recurrence	0.86*	0.31*	1	0.61*	
Withdrawal	Onset	1	-	-	0.69*	0.02
	Persistence	0.32*	1	-	0.69*	
	Recurrence	0.21*	-0.20*	1	0.06	
Tolerance	Onset	1	-	-	0.82*	0.50
	Persistence	0.44*	1	-	0.79*	
	Recurrence	0.82*	0.46*	1	0.72*	
Physical/ Psychological	Onset	1	-	-	0.79*	0.10
	Persistence	0.46*	1	-	0.76*	
	Recurrence	0.36*	-0.02	1	0.20*	
Time Spent	Onset	1	-	-	0.88*	0.41
	Persistence	0.22*	1	-	0.55*	
	Recurrence	0.83*	0.20*	1	0.74*	
Social Problems	Onset	1	-	-	0.78*	0.40
	Persistence	0.40*	1	-	0.54*	
	Recurrence	0.72*	0.16	1	0.55*	
Failure To Fulfill	Onset	1	-	-	0.89*	0.15
	Persistence	0.20*	1	-	0.41*	
	Recurrence	0.50*	0.01	1	0.49*	
Give Up	Onset	1	-	-	0.89*	0.24
	Persistence	0.29*	1	-	0.46*	
	Recurrence	0.54*	0.08	1	0.49*	

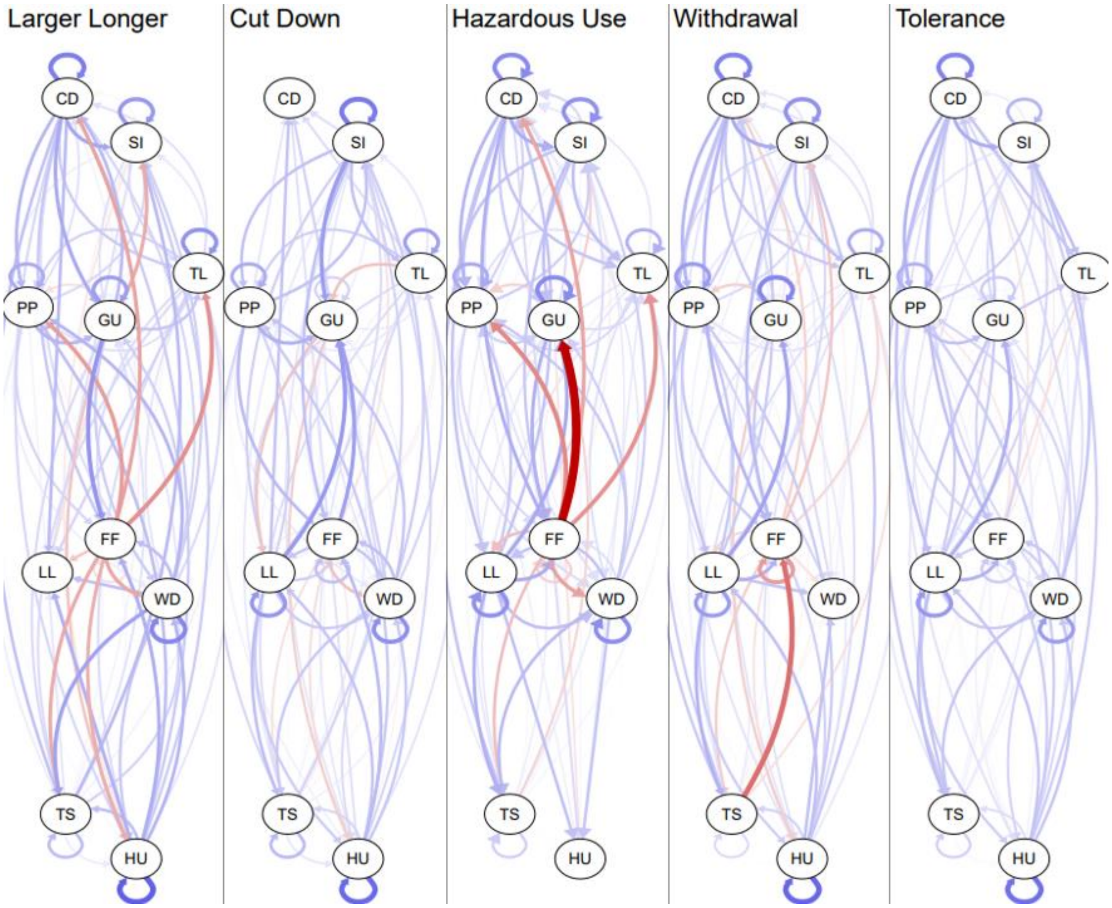
Note. Pearson correlation coefficients for edge weights between each course network and the unconditioned network. Final column lists the intraclass correlation coefficient for reliability of the onset, persistence, and recurrence networks. ICC=Intraclass Correlation Coefficient.

Table 4.
Proportion of Edge Agreement

	Course Networks	Course + Unconditioned Networks	Pairwise Edge Agreement (Kappa)	Onset	Persistence	Recurrence	Unconditioned
Aggregate	0.57	0.44	Onset	-	0.17	0.54	0.15
			Persistence	0.17	-	0.15	-0.15
			Recurrence	0.54	0.15	-	0.21
Larger/Longer	0.54	0.53					
Cut Down	0.61	0.61					
Hazardous Use	0.60	0.59					
Withdrawal	0.52	0.52					
Tolerance	0.67	0.67					
Physical/Psych	0.53	0.52					
Time Spent	0.56	0.56					
Social Problems	0.53	0.53					
Failure To Fulfill	0.48	0.48					
Give Up	0.42	0.42					

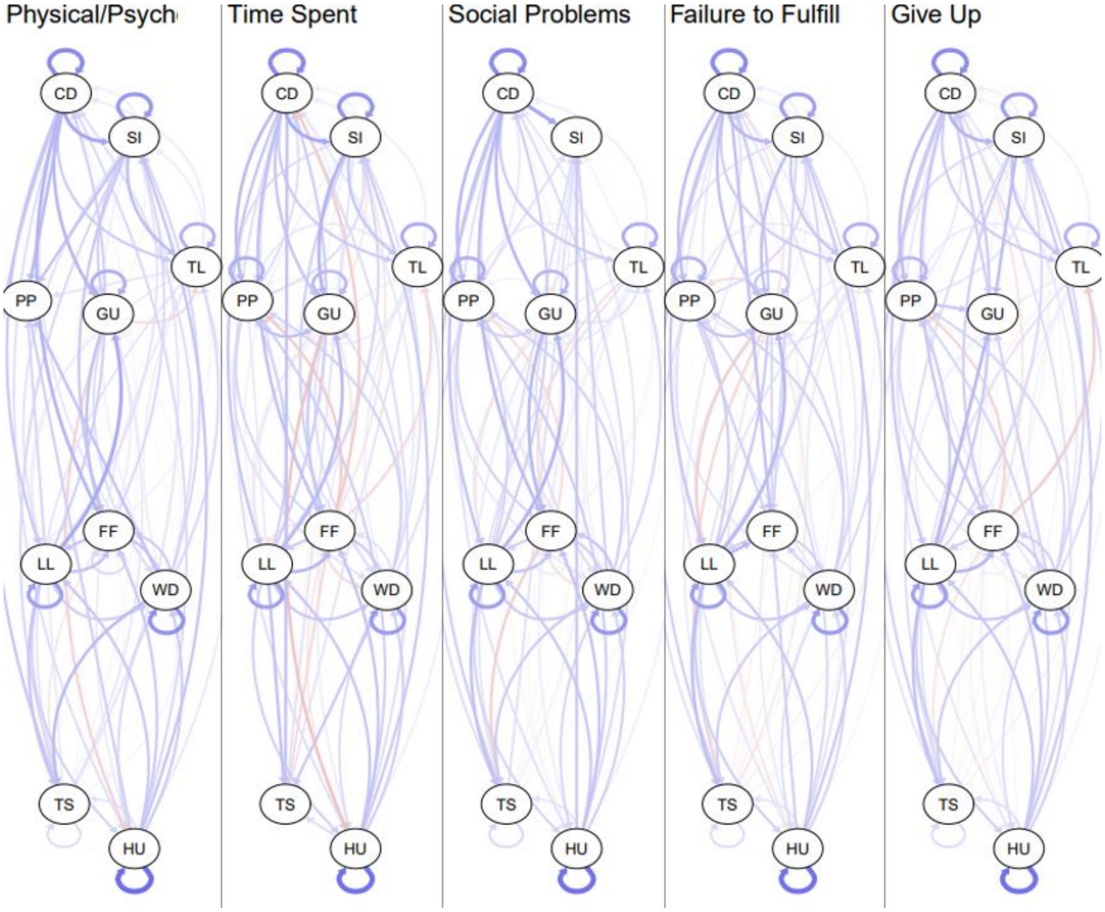
Note. Proportion of edges that directionally replicated (all edge weights > 0 or all edge weights < 0) in across all networks. Pairwise agreement between aggregate network edges was estimated with Cohen's Kappa.

Figure 1.
Onset Networks 1-5



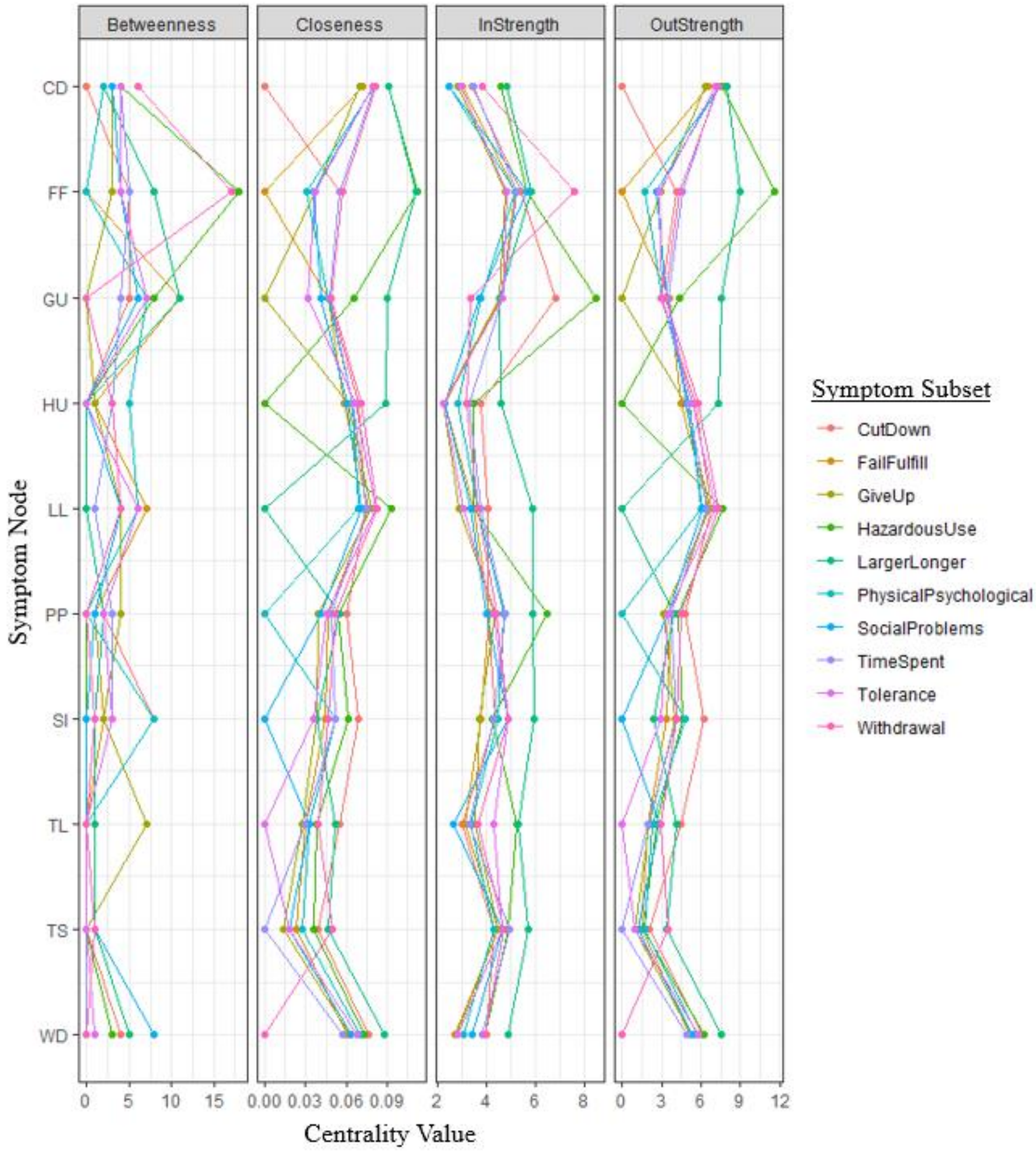
Note. Results from cross-lagged panel network models subset on symptom onset. The label above each network indicates the symptom which the data was subset on, and networks are ordered by sample size, starting with the largest sample. Blue lines indicate positive edges, red lines indicate negative edges, and line thickness indicates the strength of the relationship. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 2.
Onset Networks 6-10



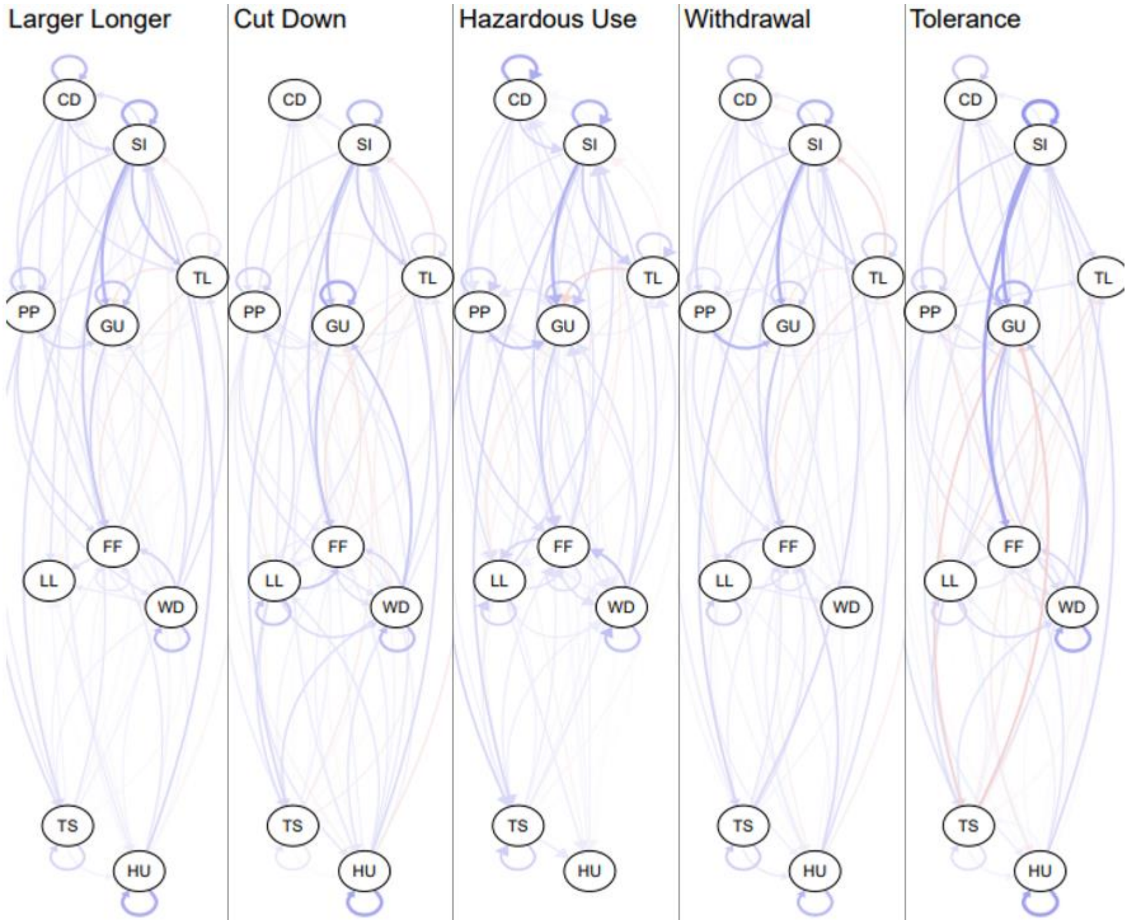
Note. Results from cross-lagged panel network models subset on symptom onset. The label above each network indicates the symptom which the data was subset on, and networks are ordered by sample size, starting with the largest sample. Blue lines indicate positive edges, red lines indicate negative edges, and line thickness indicates the strength of the relationship. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 3.
Onset Centrality



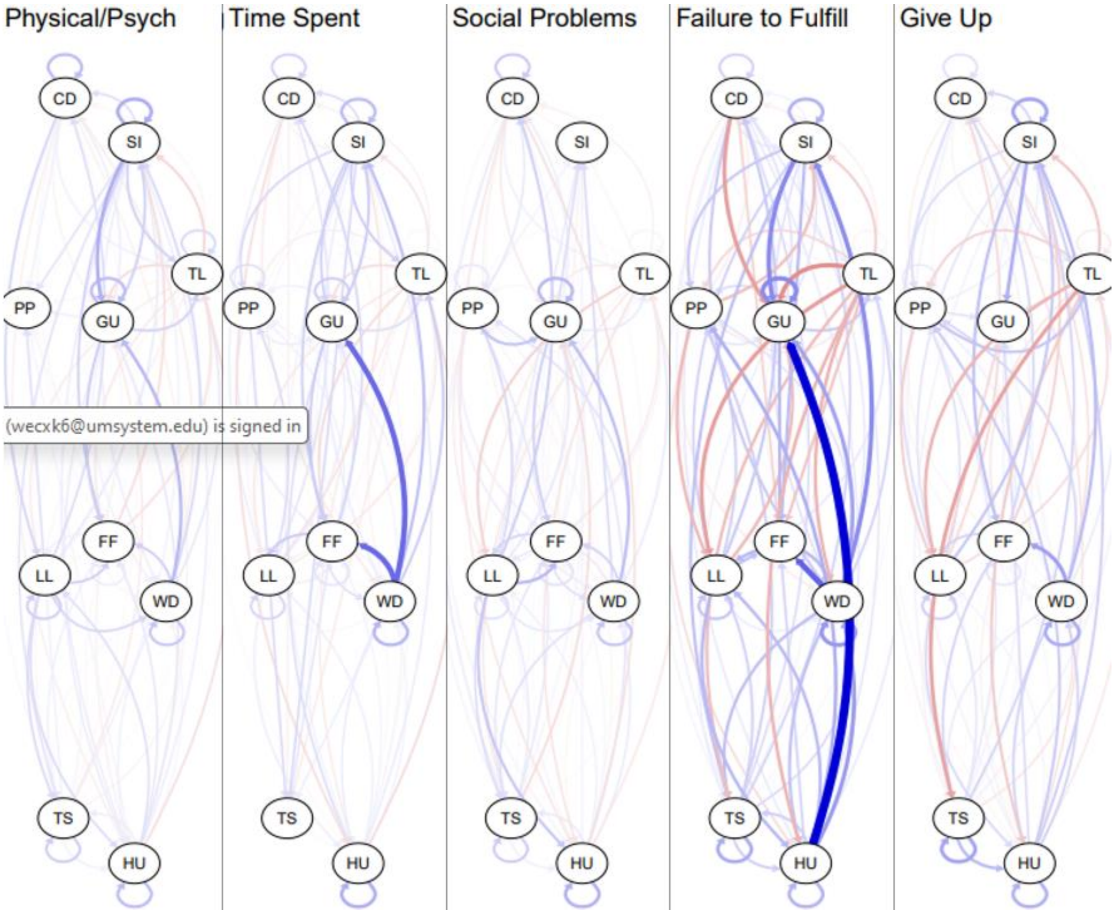
Note. Figure displays the centrality values for each node in each of the 10 symptom onset networks. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 4.
Persistence Networks 1-5



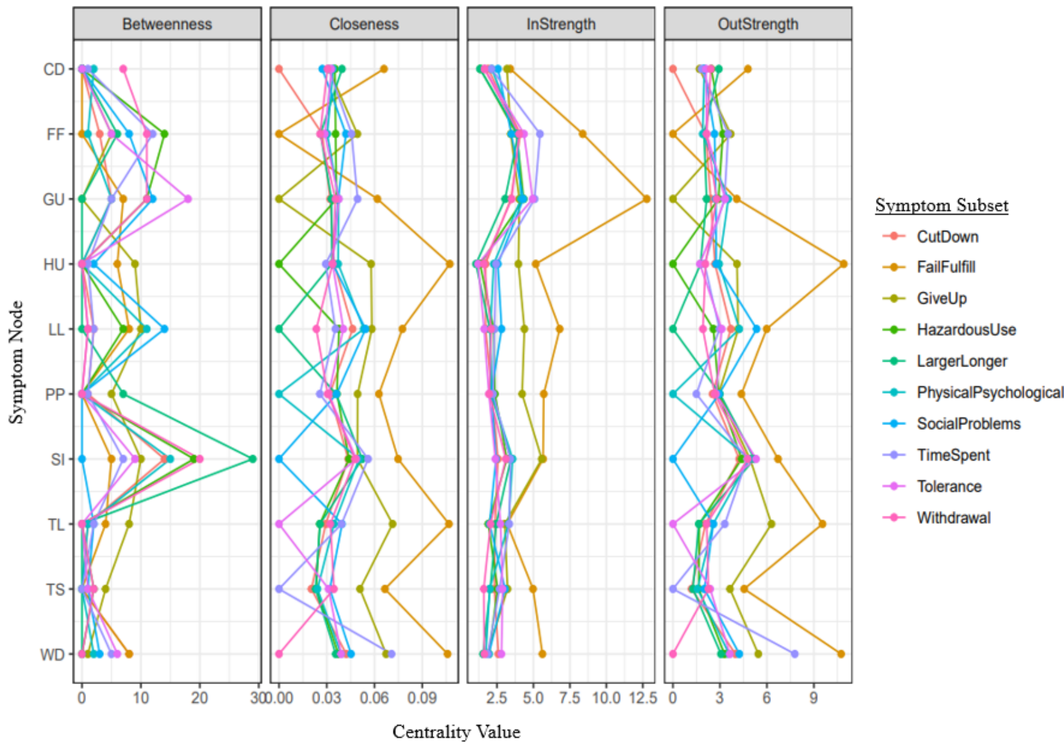
Note. Results from cross-lagged panel network models subset on symptom persistence. The label above each network indicates the symptom which the data was subset on, and networks are ordered by sample size, starting with the largest sample. Blue lines indicate positive edges, red lines indicate negative edges, and line thickness indicates the strength of the relationship. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 5.
Persistence Networks 6-10



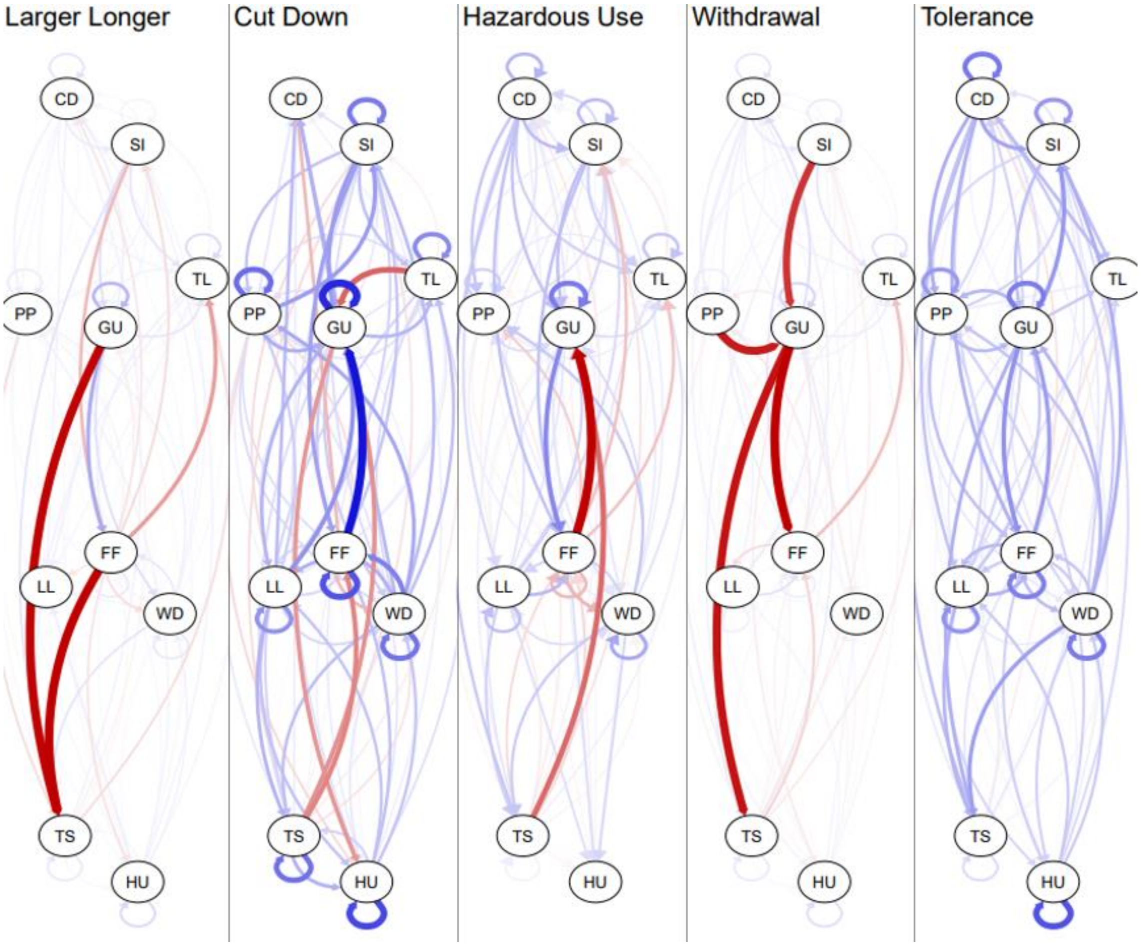
Note. Results from cross-lagged panel network models subset on symptom persistence. The label above each network indicates the symptom which the data was subset on, and networks are ordered by sample size, starting with the largest sample. Blue lines indicate positive edges, red lines indicate negative edges, and line thickness indicates the strength of the relationship. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 6.
Persistence Centrality



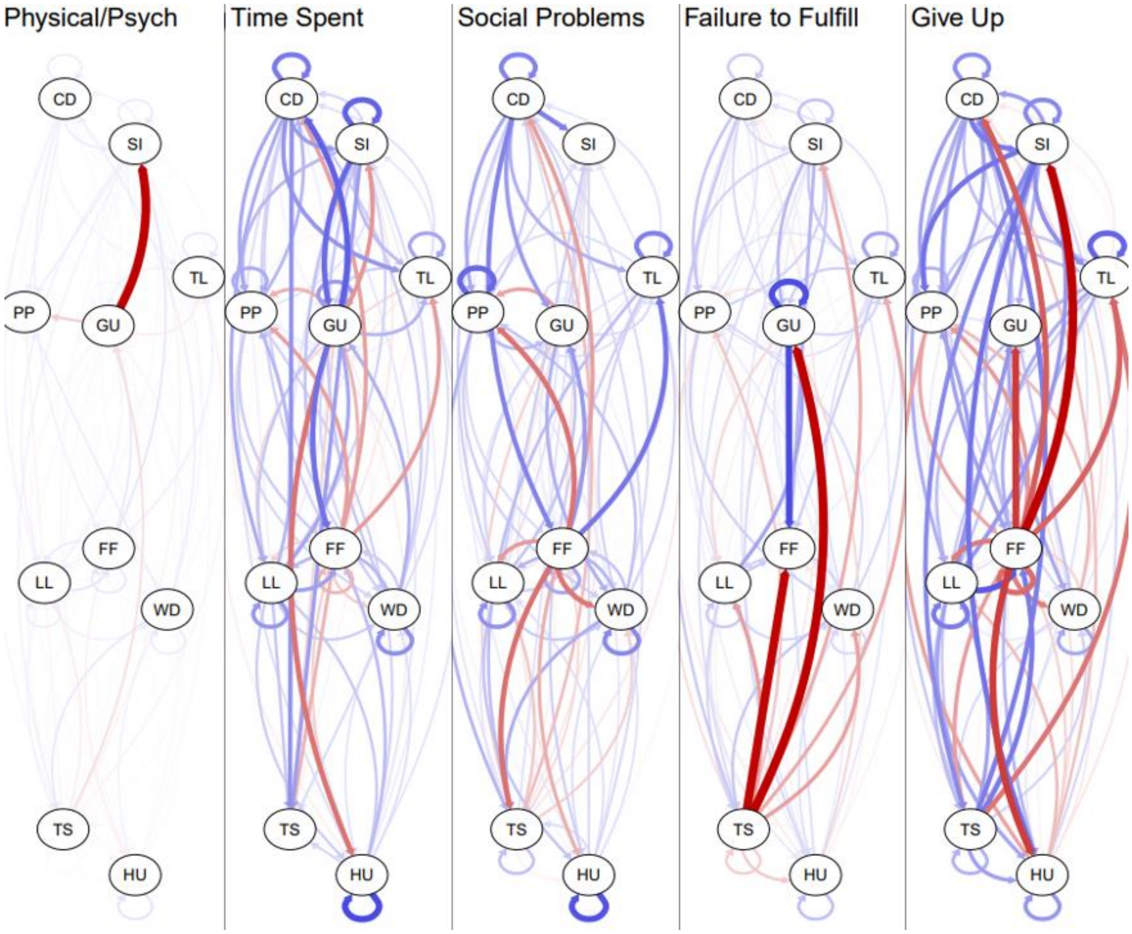
Note. Figure displays the centrality values for each node in each of the 10 symptom persistence networks. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 7.
Recurrence Networks 1-5



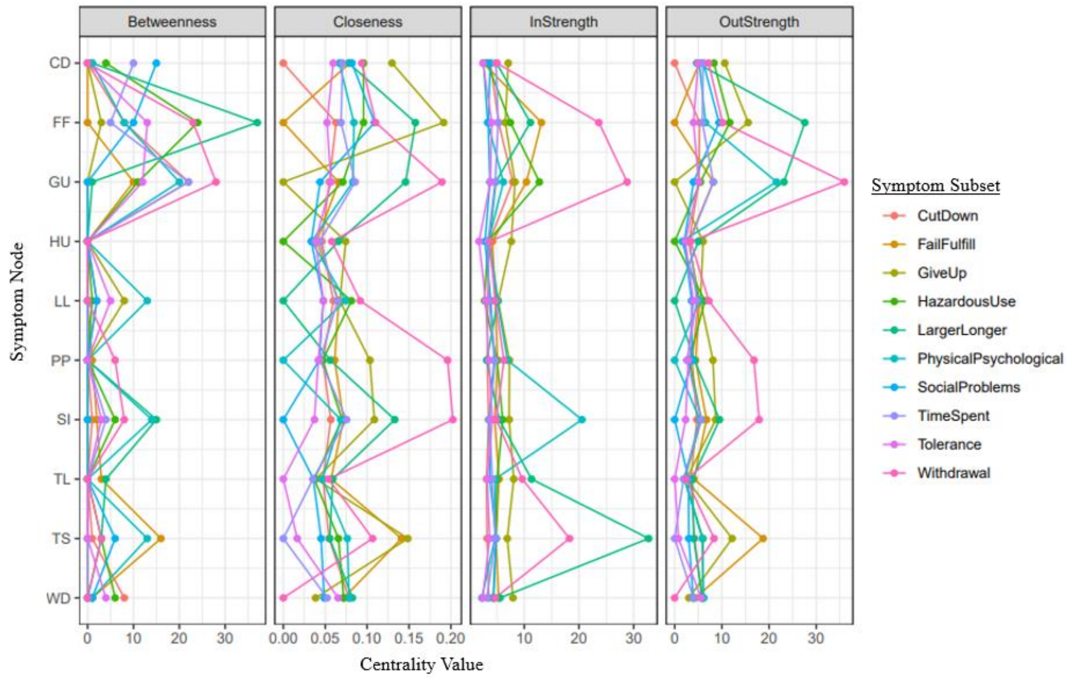
Note. Results from cross-lagged panel network models subset on symptom recurrence. The label above each network indicates the symptom which the data was subset on, and networks are ordered by sample size, starting with the largest sample. Blue lines indicate positive edges, red lines indicate negative edges, and line thickness indicates the strength of the relationship. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 8.
Recurrence Networks 6-10



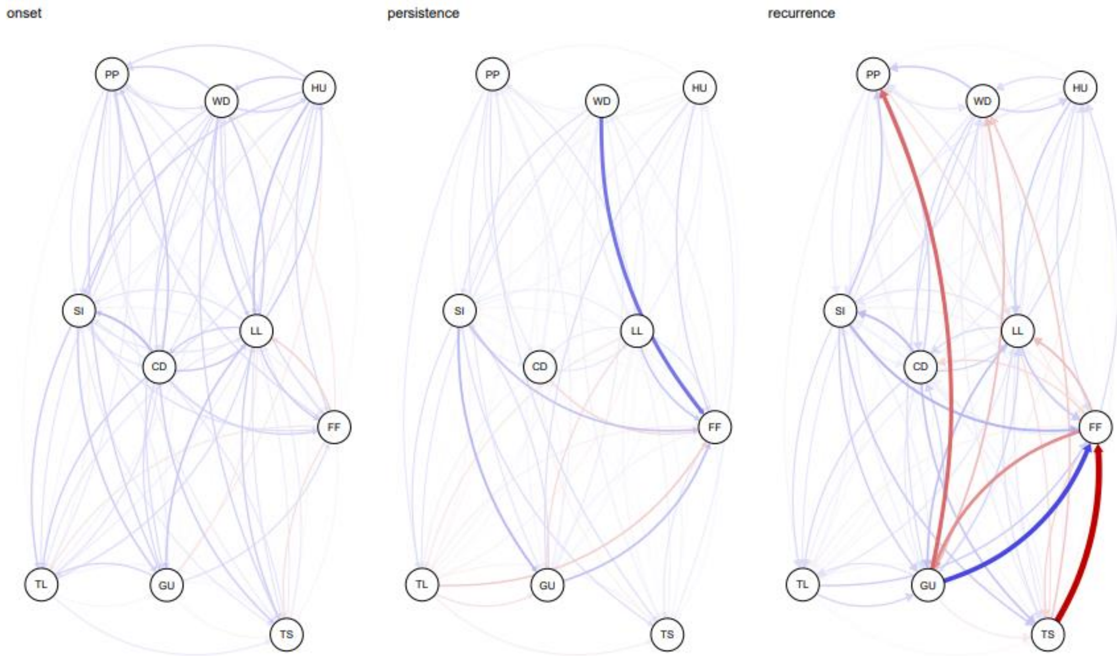
Note. Results from cross-lagged panel network models subset on symptom recurrence. The label above each network indicates the symptom which the data was subset on, and networks are ordered by sample size, starting with the largest sample. Blue lines indicate positive edges, red lines indicate negative edges, and line thickness indicates the strength of the relationship. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 9.
Recurrence Centrality



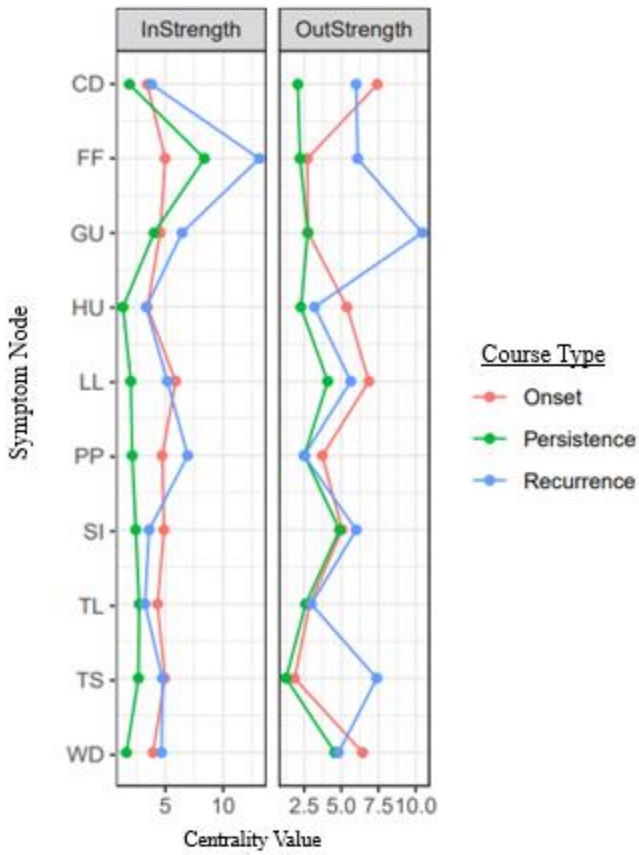
Note. Figure displays the centrality values for each node in each of the 10 symptom recurrence networks. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 10.
Aggregate Network Models



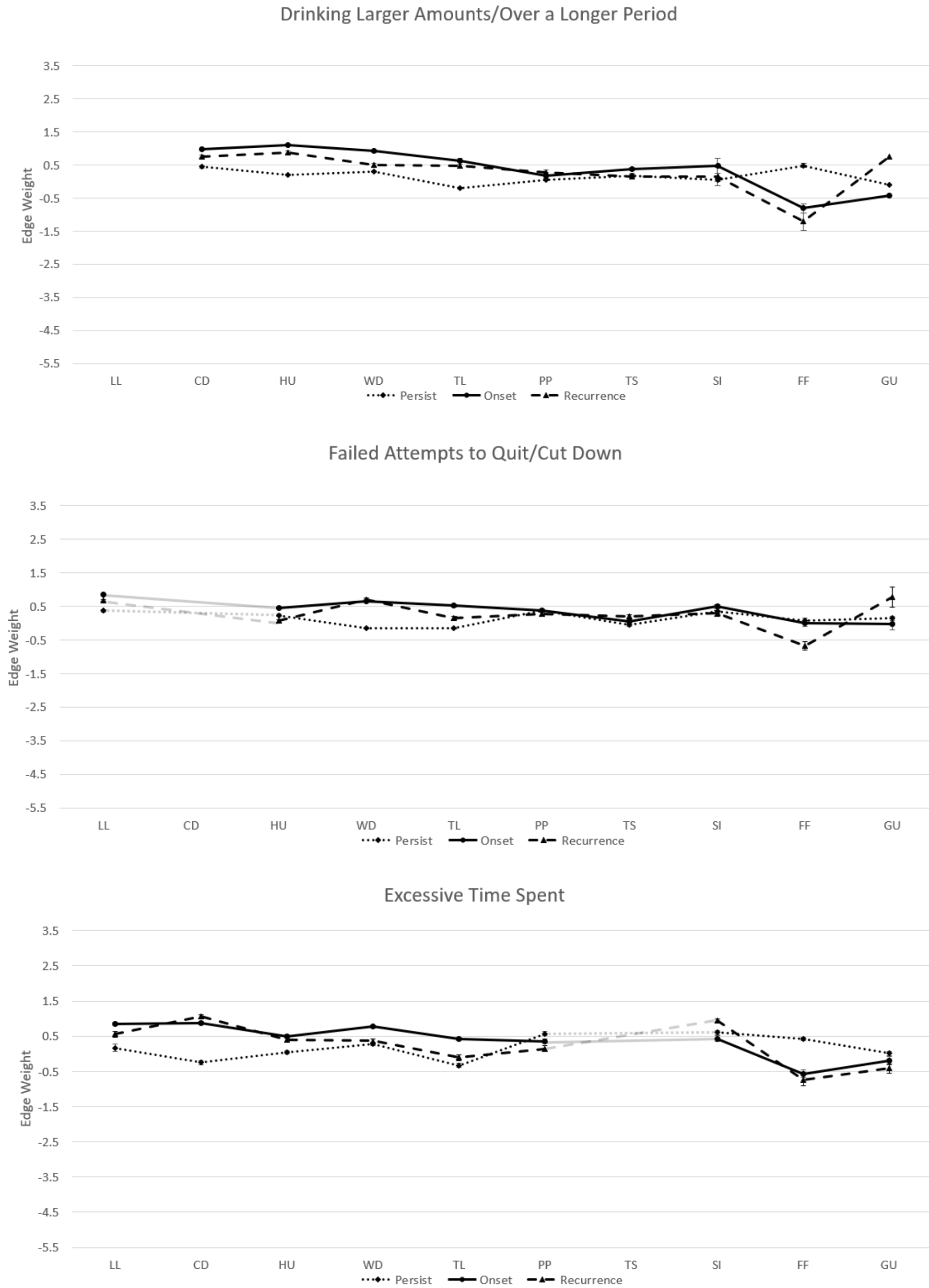
Note. These symptom networks consist of the edges extracted from each of the 10 networks associated with a given stage of course. As such, each node has a different sample size, and is limited in its interpretability via network theory. This figure primarily functions as a condensed "snapshot" of the relevant edges from the course networks that measure the course of each symptom. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 11.
Aggregate Network Centrality



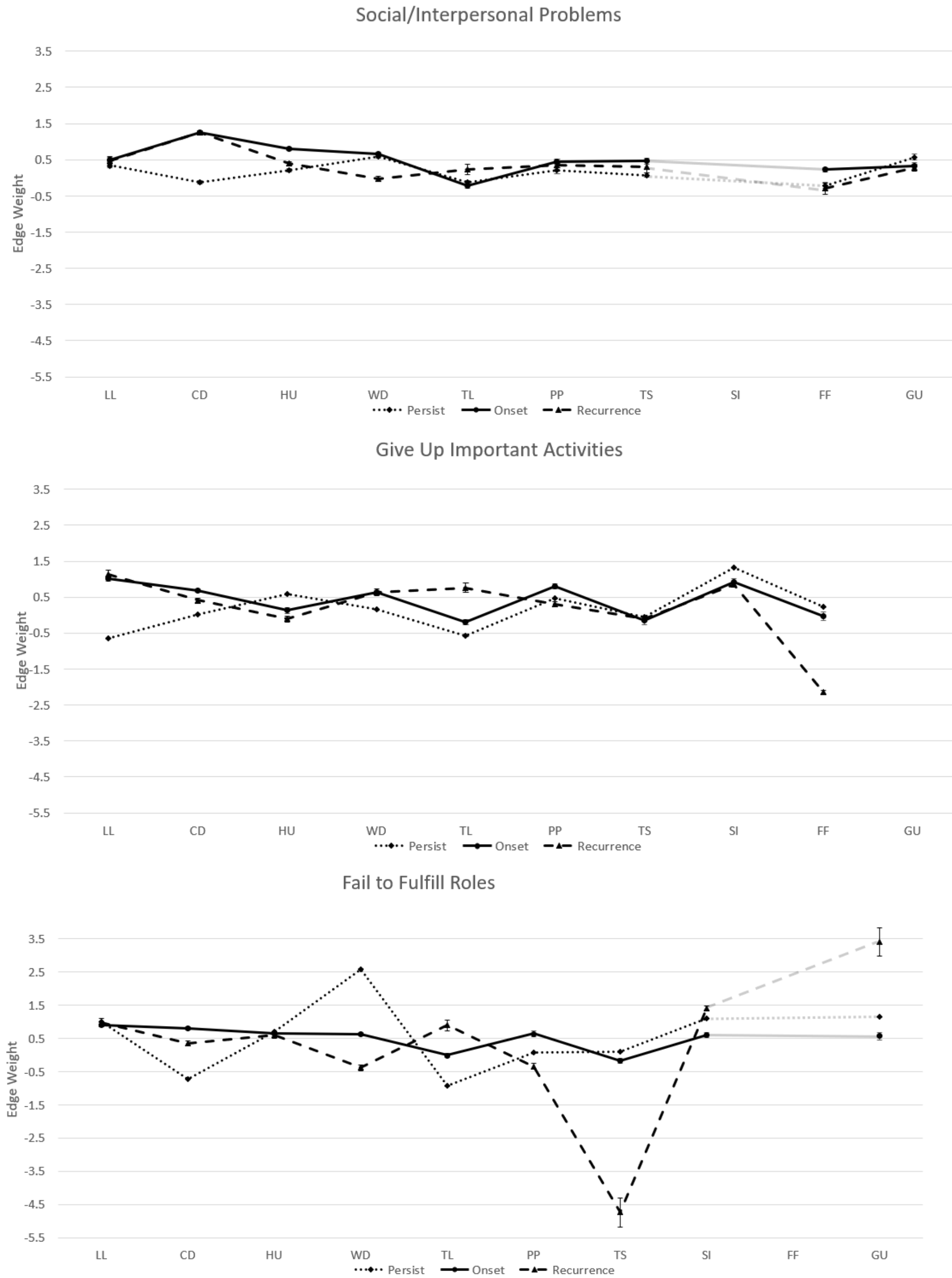
Note. Figure displays the strength centrality values for each node in the aggregate Onset, Persistence, and Recurrence networks. Points are a summarized version of Figures 3, 6, and 9, plotting the strength of influence each symptom has on the course of other symptoms (outsterngth) and the strength of influence that other symptoms have on the course of each symptom (instrength). CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 12.
Impaired Control Edge Weights



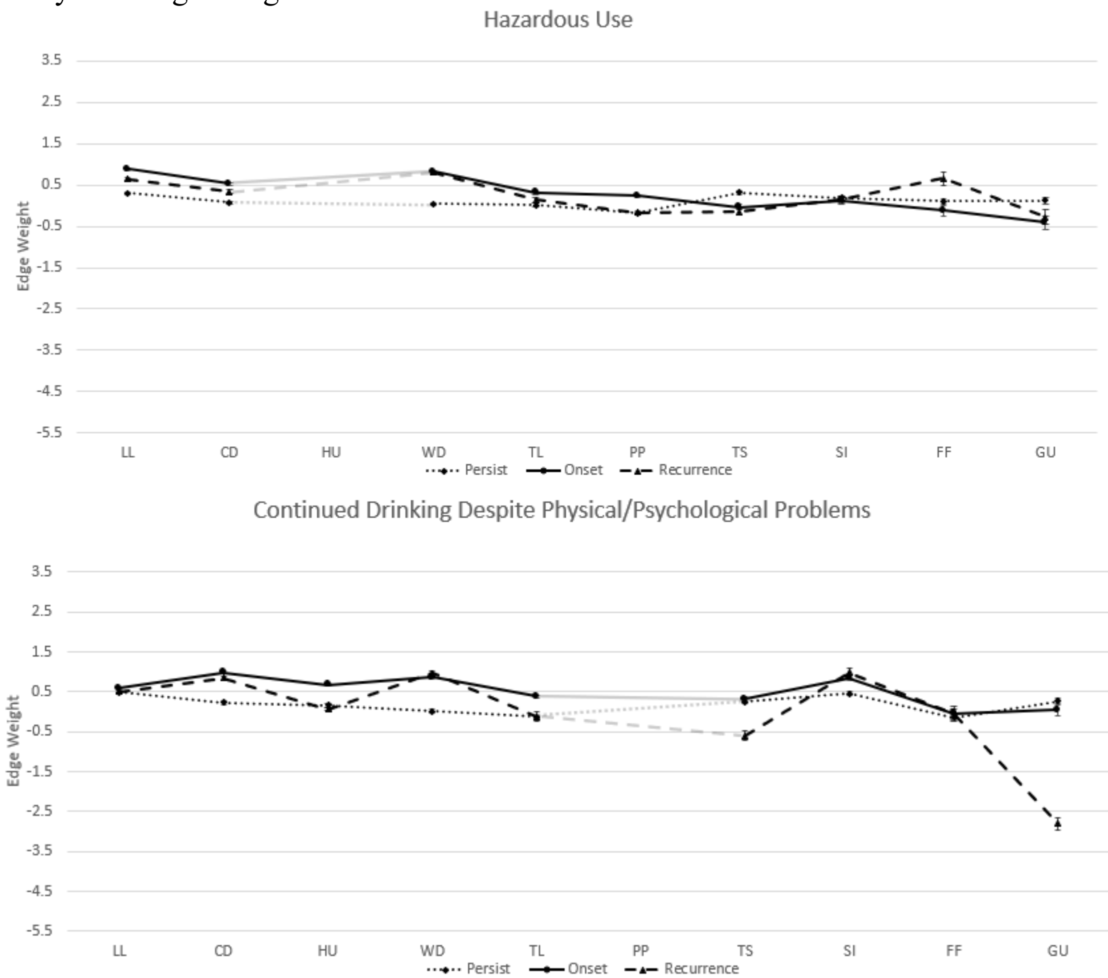
Note. Figure displays the extent to which each symptom influences the course of the symptom in the title of the plot. Points and error bars represent the estimate of each edge weight. Autoregressive estimates cannot be produced in course analyses and are overlayed in grey. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 13.
Social Impairment Edge Weights



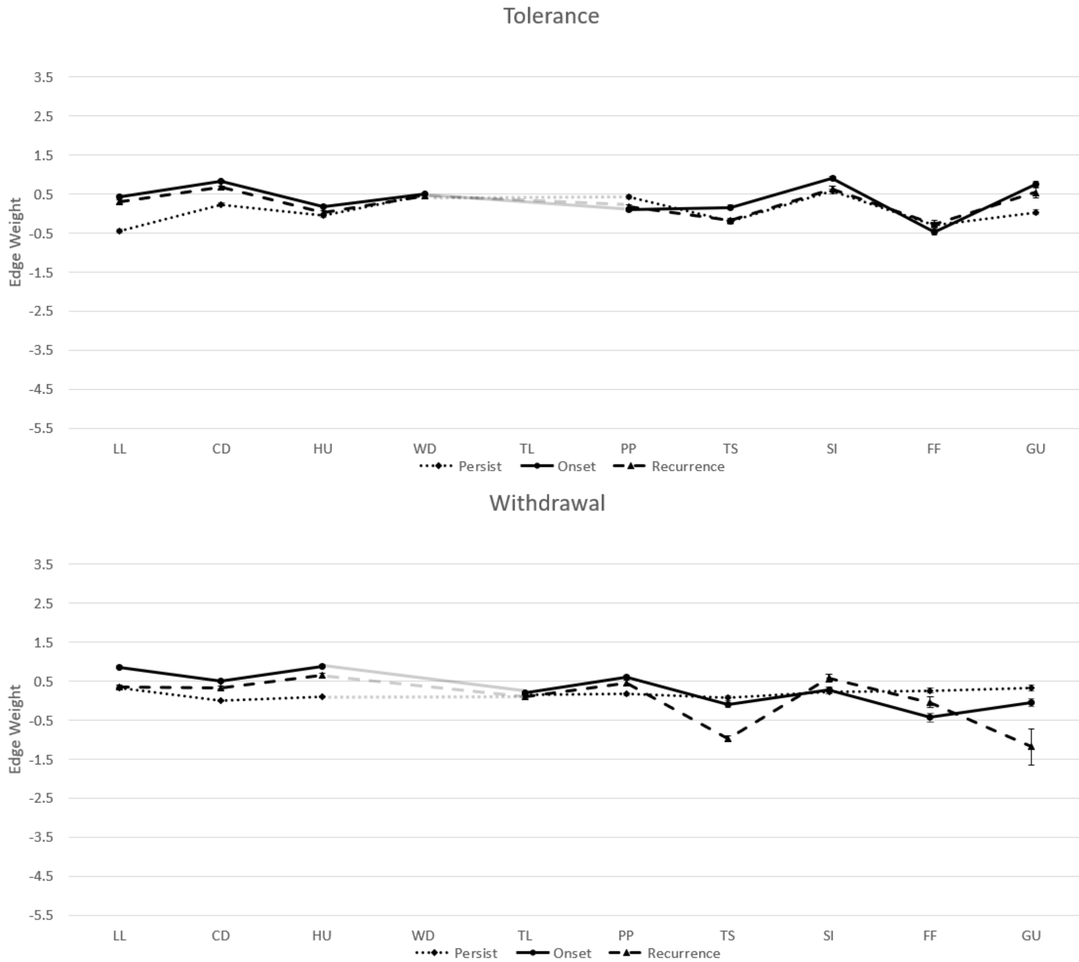
Note. Figure displays the extent to which each symptom influences the course of the symptom in the title of the plot. Points and error bars represent the estimate of each edge weight. Autoregressive estimates cannot be produced in course analyses and are overlayed in grey. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 14.
Risky Use Edge Weights



Note. Figure displays the extent to which each symptom influences the course of the symptom in the title of the plot. Points and error bars represent the estimate of each edge weight. Autoregressive estimates cannot be produced in course analyses and are overlayed in grey. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

Figure 15.
Pharmacological Criteria Edge Weights



Note. Figure displays the extent to which each symptom influences the course of the symptom in the title of the plot. Points and error bars represent the estimate of each edge weight. Autoregressive estimates cannot be produced in course analyses and are overlayed in grey. CD=Cut Down, FF=Failure to Fulfill, GU=Give Up, HU=Hazardous Use, LL=Larger/Longer, PP=Physical/Psychological Problems, SI=Social/Interpersonal Problems, TL=Tolerance, TS=Time Spent, WD=Withdrawal.

VITA

William E. Conlin was born in Payson, Arizona to his parents, Thomas and Pamela Conlin and was raised in the unincorporated town of Star Valley, Arizona. He moved to Phoenix, Arizona at age 17 and worked in the restaurant industry before deciding to go back to school at Scottsdale Community College in 2014. In 2018, he received a Bachelor of Arts in Psychology from Arizona State University and was accepted into the Clinical Psychology doctoral program at the University of Missouri to work with Dr. Kenneth Sher. He received his Master of Arts degree in 2020 and completed the requirements for a quantitative minor in psychological statistics in 2023.